This document was submitted to EPA by a registrant in connection with EPA's evaluation of this chemical, and it is presented here exactly as submitted.

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07/ORP 41203

Dow AgroSciences

308, 2A
October 19, 1999

***via Fax:* 703-308-8041**
Mr. Mark Hartman
Product Manager
Special Review and Reregistration Division
United States Environmental Protection Agency
401 M Street, S.W.
Washington, DC 20460

Dear Mr. Hartman:

Pursuant to your phone message, Dow AgroSciences would like to clarify issues regarding confidentiality of our responses to the chlorpyrifos preliminary risk assessment documents. As stated in our responses, and again in our letter of October 15 to Ms. Marcia Mulkey, Dow AgroSciences makes no claims of confidentiality to our submission entitled *Dow AgroSciences' Response to U.S. EPA's Preliminary Risk Assessment for Chlorpyrifos, Health Effects Division Chapter Dated July 23, 1999*, and *Dow AgroSciences' Response to U.S. EPA's Draft Reregistration Eligibility Science Chapter for Chlorpyrifos, Fate and Environmental Risk Assessment Chapter Dated November 24, 1998*. As such, we request a docket classification of "A" for both of the aforementioned submissions.

Sincerely,

F. M. Gersich

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STUDY TITLE

Dow AgroSciences' Response to U.S. EPA's Preliminary Risk Assessment for Chlorpyrifos, Health Effects Division Chapter Dated July 23, 1999

DATA REQUIREMENT

None

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STUDY COMPLETED ON

2-September-1999

PERFORMING LABORATORY

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LABORATORY STUDY ID

GH-C 4958

STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS

Compound: Chlorpyrifos

Title: Dow AgroSciences' Response to U.S. EPA's Preliminary Risk Assessment for Chlorpyrifos, Health Effects Division Chapter Dated July 23, 1999

No claim of confidentiality is made for any information contained in this study on the basis of its falling within the scope of FIFRA Section 10 (d)(1)(A), (B), or (C)*.

Company: Dow AgroSciences LLC

Company Agent: Robert F. Bischoff

Title: Regulatory Manager

Signature: _____

Date: _____

*In the United States, the above statement supersedes all other statements of confidentiality that may occur elsewhere in this report.

THIS DATA MAY BE CONSIDERED CONFIDENTIAL IN COUNTRIES OUTSIDE THE UNITED STATES.

STATEMENT OF COMPLIANCE WITH GOOD LABORATORY PRACTICE STANDARDS

Title: Dow AgroSciences' Response to U.S. EPA's Preliminary Risk Assessment for Chlorpyrifos, Health Effects Division Chapter Dated July 23, 1999

Study Completion Date: 2-September-1999

This study does not meet the definition of a GLP study as it appears in:

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Executive Summary

Dow AgroSciences LLC (DAS) is respectfully submitting comments in response to a request from the EPA to review the preliminary human risk assessment for chlorpyrifos. This draft assessment is comprised of a memorandum entitled "Chlorpyrifos: HED Preliminary Risk Assessment for the Reregistration Eligibility Decision (RED) Document. Chemical No. 059101. Barcode: D257953," Deborah C. Smegal, July 23, 1999, and 16 attachments:

1. Toxicology Chapter (5/6/99)
2. Chlorpyrifos Re-Evaluation – Report of the Hazard Identification Assessment Review Committee (12/7/98)
3. Report of the FQPA Safety Factor Committee (4/5/99)
4. Replacement of Human Study Used in Risk Assessment (6/2/99)
5. Acute Dietary Risk Assessment for Chlorpyrifos (7/22/99)
6. Chronic Non-Cancer Dietary Exposure Assessment for Chlorpyrifos (6/1/99)
7. Anticipated Residues for Chronic Dietary Exposure Assessment for Chlorpyrifos RED (6/1/99)
8. Chlorpyrifos. Possible Reduction of Residue Studies (4/7/95)
9. Revised Product and Residue Chemistry Chapter (5/25/99)
10. Drinking Water Assessment of Chlorpyrifos (11/13/98)
11. Agricultural and Occupational Exposure Assessment (7/22/99)
12. Occupational/Residential Handler and Post-Application Residential Risk Assessment (6/30/99)
13. Chlorpyrifos Incident Review Update (6/30/99)
14. Update of Incident Data on Chlorpyrifos for Domestic Animals (4/26/99)
15. Analysis of Chlorpyrifos IDS Data for Domestic Animals (1/23/95)
16. Status of HED-Related Dow AgroSciences Study Submissions that Impact the HED Preliminary Risk Assessment (5/28/99)

Chlorpyrifos products have been extensively researched and tested, and DAS continues to update that scientific database each year. More than 3,600 studies and reports have been provided to

EPA in support of its continued registration. Three decades of use have shown that unless seriously misused, chlorpyrifos products have wide margins of safety that protect users and consumers, including infants and children.

The EPA's preliminary risk assessment for chlorpyrifos contains numerous errors and omissions of fact and is premised on fundamental errors of science and law. These errors include use of highly unorthodox and largely unsupported science policy decisions that reject the use of or failure to consider reliable and available data, ignore prevailing scientific and regulatory consensus, and are inconsistent with precedent established by EPA, FDA, and other internationally recognized risk assessment bodies.

The EPA's preliminary risk assessment is so misleading as to the potential risks posed by chlorpyrifos that its release without substantial revision would be irresponsible and contrary to the public interest, and would constitute an indictment of the compound without the valid scientific evidence required by law.

Hazard Identification, Endpoint Selection and Food Quality Protection Act (FQPA) Safety Factor

- **Use of human study data is scientifically the most justifiable approach for deriving no observed effect levels (NOELs) for human risk assessment, provided the studies were appropriately conducted.** The EPA has proposed to change the longstanding endpoint for risk assessment of chlorpyrifos from inhibition of human plasma cholinesterase (ChE) to inhibition of animal plasma ChE, and in so doing has added a default of 10x as an interspecies uncertainty factor. The Agency is reducing the RfDs for chlorpyrifos not because of newer or more relevant data, but, in fact, is taking a step backwards by failing to consider the most relevant human data from three studies, including one completed in 1999. The available human data were developed in compliance with the provisions of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Section 12(a)(2)(P) and 40 Code of Federal Regulations (CFR) Part 26. The EPA's failure to consider these data is all the more troubling in light of Agency guidance that expressly approves the use of human data and recognizes its

unique value in the risk assessment process. (Final Guidelines for Neurotoxicity Risk Assessment, 63 FR 26925, 26933 (May 14, 1998)). This failure to consider available data is a violation of Section 408 of the Federal Food, Drug and Cosmetic Act which requires that EPA consider all available data that is relevant to a determination of safety. Further, the Agency's refusal to consider studies which were previously submitted and, until recently, formed the basis for earlier chlorpyrifos risk assessments is a denial of DAS' due process rights with respect to data in which it holds a valuable and judicially recognized property interest.

- **Human red blood cell (RBC) acetylcholinesterase (AChE) data or animal brain AchE data should be used as the basis for endpoint selection.** Plasma cholinesterase provides a measure of exposure, not of toxicity. If human data are available, RBC results provide a more reliable predictor for central nervous system (CNS) and peripheral nervous system (PNS) toxicity, and available animal data show that RBC is a conservative endpoint (i.e., effects on RBC consistently appear at lower or similar doses to those affecting brain AChE). The chlorpyrifos RfD should be based on human RBC AchE inhibition rather than animal plasma ChE inhibition. Plasma ChE inhibition is not an adverse effect and it should not be considered as a critical effect for the purpose of setting chlorpyrifos RfDs. Acute and chronic RfDs should be established at 0.05 mg/kg and 0.01 mg/kg/day, respectively, for dietary, occupational and residential exposures to chlorpyrifos. These values are consistent with those currently utilized by the World Health Organization (WHO), the European Union (EU), Canada and the State of California.
- **Humans are not more sensitive to the cholinesterase inhibition produced by chlorpyrifos than are animals**. When the same endpoint is considered, studies show a similar dose-response and NOELs for chlorpyrifos in humans, non-human primates, dogs, rats and mice. The extensive database on chlorpyrifos shows that animals are either equally affected or more sensitive than humans. The animal studies strongly support the position that inhibition of human RBC AChE is the appropriate endpoint for chlorpyrifos hazard evaluation and risk assessment. However, if EPA continues to propose the use of animal data to set RfDs for chlorpyrifos, then the tenfold interspecies uncertainty factor (UF) is clearly not

needed because no difference in relative sensitivity can be demonstrated for animals versus humans.

- **There is no justification for retention of a 3x FQPA safety factor for chlorpyrifos.** An additional margin of safety is required under Section 408(b)(2)(C) of the Federal Food, Drug and Cosmetic Act "to take into account potential pre- and post-natal toxicity and completeness of the data with respect to exposure to infants and children." In order to trigger the FQPA safety factor there must be both evidence of toxicity and incomplete exposure data. This interpretation of section 408 (b)(2)(C) is consistent with FIFRA's prohibition on the initiation of a public review process for a pesticide in the absence of a validated test or other significant evidence raising prudent risk concerns. The evidentiary standard contained in FIFRA Section 3(c)(8) was not amended by FQPA. In the case of chlorpyrifos, neither prong of the two-part test has been met – there is no evidence of pre-natal or post-natal toxicity nor is there an incomplete exposure data base. Neither the published literature nor Guideline developmental neurotoxicity, developmental or reproductive toxicity studies support retention of this factor. There are sufficient data to conclude that the fetus and neonate are not more sensitive to chlorpyrifos than the adult at low dose levels. In addition, potential widespread exposure cited by EPA does not meet the statutory test for application of the FQPA safety factor. The 3x FQPA safety factor can be removed because chlorpyrifos has been shown to possess no pre- or post-natal toxicity of concern at relevant human exposure conditions.
- **Numerous papers appearing in the scientific, peer-reviewed literature support the reregistration of chlorpyrifos.** DAS strongly encourages EPA to review numerous papers which have recently appeared in scientific, peer-reviewed literature which specifically address critical issues relating to the reregistration of chlorpyrifos and scientifically defensible application of FQPA mandates. For a listing of published papers, as well as a brief summary, see Appendix H.
- **An international group of experts reviewed chlorpyrifos data in light of FQPA mandates.** In October of 1998, an international group of experts in toxicology and exposure assessment gathered in Washington, DC for a conference to explore new scientific challenges under FQPA. With a rich toxicity and exposure database supporting the product, chlorpyrifos

made an excellent candidate to discuss these scientific challenges in a "real-world" context. A summary of this conference can be found in Appendix I.

Dietary Exposure and Risk Assessment

- **Acute dietary risk assessment requires further refinements.** Although the EPA has incorporated significant refinements into the acute dietary risk assessment, the Agency should continue to work toward producing more realistic acute dietary assessments. Further refinements, such as use of actual monitoring data and recognition of the potential reduction in residues from cooking, etc., are needed to produce a more realistic assessment. For example, EPA's use of eight residue data points from field trials conducted for cranberries in the acute dietary risk assessment increase the exposure values from 44 to 120% of the RfD. Use of such assumptions lead to overestimation of the acute dietary exposure to chlorpyrifos. When the questionable, default values for cranberries are removed, the acute dietary exposure at the 99.9th percentile, to chlorpyrifos is less than 50% of the EPA's proposed RfD and less than 5% of the RfD proposed by DAS for the highest exposed population. And, for the same assessment scenario, acute dietary exposure to chlorpyrifos is less than 10% of the EPA's proposed RfD and less than 1% of the RfD proposed by DAS for the highest exposed population at the 95th percentile.
- **Acute dietary exposure can not be reliably estimated at the 99.9th percentile of the exposure distribution.** For acute dietary risk assessment, the EPA presents the results obtained at the 99.9th percentile estimate of the exposure distribution. The 99.9th percentile estimates can not be reliably determined given current limitations of input values such as consumption estimates or, in some cases, field trial residue values. The Agency should consider results over a range of percentiles, such as 95 to 97.5%, as they are more realistic and scientifically defensible. The reasonable certainty of no harm standard in Section 408 of the Federal Food, Drug and Cosmetic Act is the same standard applied for 40 years by FDA for food additives under Section 409. It is clear from the legislative history and FDA's application of that standard that "reasonable certainty" does not mean absolute certainty.

EPA's use of the 99.9th percentile of exposure is a case in point. It runs counter to FDA precedent and is an arbitrary and capricious interpretation of the FQPA safety standard.

- **Default assumptions relating to chronic dietary risk estimates can not be supported by available scientific data.** EPA's default assumptions for inclusion of potential residues from treatment of food handling establishments (FHE) in the chronic dietary risk assessments increase theoretical exposures from only 25% of EPA's proposed RfD to 790%, implying exposure from indirect residues as a result of treatment of the FHE is 30 times greater than exposure as a result of direct applications to all registered crops. Available data contradicts such estimates, indicating no measurable increases in dietary exposure as a result of FHE treatments. EPA's policy, "Proposed Threshold of Regulation Policy Defining When a Food Use Does Not Require a Tolerance" on FHE also states that uses which produce no detected residues are considered "essentially zero" exposure. The FHE uses with chlorpyrifos meet this criteria.

Water Exposure

- **Drinking water exposure estimates grossly overestimate potential risk.** EPA's recommended concentrations for chlorpyrifos in drinking water are based on conservative screening model calculations not applicable to actual chlorpyrifos use, unintended events that are remediated, and overly conservative interpretation of limited non-drinking water monitoring data. Consequently, these recommended concentration estimates are unreliable and inappropriate for human health risk assessment.
- **Recent monitoring data need to be considered.** A recent submission of the occurrence of chlorpyrifos in waters of the United States confirms the low level of detections in surface and groundwater and demonstrates no detections in drinking water. Additionally, DAS is presently conducting, with four industry partners, a prospective community water system surface drinking water monitoring study for chlorpyrifos and will communicate the results to the Agency for risk refinement.

Agricultural, Occupational and Residential Exposure and Risk Assessment

- **Risk assessments should reflect real world exposure scenarios.** EPA conducted numerous risk assessments on product use scenarios that are inaccurate reflections of actual use in the marketplace, thus generating exposure scenarios that are not reflective of real world exposure and risk. Many of the risk assessments conducted by EPA were based on formulations and labels not currently available or utilized in the marketplace. Many of the risk assessments of non-agricultural uses conducted by EPA were based on product use inputs taken from generic insecticide use databases or extrapolated from agricultural use scenarios which overestimate the actual exposure and risk of these products. To help provide a better understanding of actual chlorpyrifos non-agricultural market usage and allow more refined assessments, DAS is submitting data from a market research study completed in 1999.
- **Occupational and residential exposures do not exceed the human data based level of concern.** DAS believes the assessment of occupational and residential exposures to chlorpyrifos should be based on the use of NOELs established from studies in humans. This would result in a NOEL of 0.5 mg/kg/day for the short-term exposure and 0.1 mg/kg/day for intermediate- and long-term exposure scenarios, and would negate the need for the 10x interspecies factor. Therefore, margins of exposure (MOE) above 10 would represent acceptable and safe margins. Occupational and residential exposures of chlorpyrifos do not exceed the human data based level of concern (MOE of 10) for short-, intermediate- or long-term exposure for all the use scenarios of chlorpyrifos.
- **Methodologies used to assess occupational and residential exposures need refinement.** The methodologies used to assess occupational and residential exposures represent early-stage assessments. Further refinement toward more realistic estimates may be possible through higher-tier approaches and techniques such as Monte Carlo assessment.
- **DAS commits effort in developing standard operating procedures (SOP) for residential exposure assessment.** Ongoing initiatives may have significant impact on the draft SOP for residential exposure assessment. SOPs used are still only in the formative, draft stage and have not received final approval. DAS has dedicated significant time and resources through

involvement with ongoing task forces to develop data and/or refine the SOPs. Any assessments using current draft SOPs should be considered preliminary and conservative.

Incident Review

- **Selective consideration of available incident information results in biased conclusions.** DAS is very concerned about the selective use of data and information in the Agency's report entitled "Chlorpyrifos Incident Review." Since 1996, DAS has operated an expanded human inquiry/incident product stewardship program. This program was initiated as part of the "10 Point Plan" on chlorpyrifos agreed to by both the Agency and DAS, and is provided through independent experts in poison control that are also affiliated with the University of Minnesota (Goldman, 1997). The data obtained under this program addresses significant limitations relating to incident data available from other sources. DAS has devoted considerable resources and effort to comply with this element of the "10 Point Plan." EPA's failure to consider this data is a clear violation of the "10 Point Plan" agreement with DAS.
- **EPA's methodology for evaluation of incident reports lacks scientific rigor.** In a recent summary judgement by the District Court for the Sixth Judicial Court, St. Louis County (Duluth) Minnesota, the Court found similar incident reviews by EPA to be "scientifically unreliable" consisting of "anecdotal information gathered pursuant to a methodology not generally accepted in either the scientific or medical communities as a mechanism to establish a cause and effect relationship between chemical exposure and neurological health problems…"
- **Speculation by EPA that incident data may be suggestive of specific health issues is unsubstantiated.** Two panels of international scientific, medical and epidemiological experts (Clegg et al., 1999; Albers et al., 1999) concluded, after examining the relevant data, that chlorpyrifos had not been shown to be a concern for public health. The panels examined available scientific evidence on a variety of neurological, behavioral, and immunological disorders, multiple complaints (often called multiple chemical sensitivities (MCS or MCSS), and birth defects. After extensive review, the panels were not persuaded that exposure to chlorpyrifos-containing products caused any of these conditions in humans. The panels'

reports were submitted to the EPA in 1997 and published in peer-reviewed scientific literature in 1999.

Biomonitoring, Cumulative Exposure and Aggregate Risk Assessment

- **TCP measurements overestimate actual chlorpyrifos exposure.** Although urinary 3,5,6-trichloro-2-pyridinol (TCP) can be used to estimate potential chlorpyrifos exposure levels, some portion of those measured levels is likely due to exposure to chlorpyrifos-methyl and/or TCP itself. Therefore, direct extrapolations from measured TCP levels back to possible chlorpyrifos exposures should be recognized as very conservative, worst case estimates, and the potential contribution to TCP levels from these other sources should be excluded when drawning conclusions about possible health risks.
- **Not all OP pesticides cause adverse effects with a common mechanism of toxicity.** DAS disagrees with EPA that all organophosphorus (OP) pesticides caused adverse effects with a common mechanism of toxicity. The U.S. FIFRA Science Advisory Panel (SAP) has concluded that while all OP pesticides may inhibit AchE activity, there are other factors [pharmacokinetic (PK) and pharmacodynamic (PD) events] operating in the body that affect the toxicity of OP pesticides. Data have shown there are PK and PD actions operating which lower the toxicity induced by chlorpyrifos.
- **DAS has previously submitted an aggregate assessment showing exposures from all uses of chlorpyrifos are within acceptable limits.** DAS is awaiting Agency comments on this assessment.

In conclusion, EPA's preliminary risk assessment on chlorpyrifos contains significant errors and omissions that overestimate both exposure and risk. DAS's risk assessment correcting for Agency errors and using appropriate assumptions and data shows there is no undue risk with the labeled use of chlorpyrifos.

I. Introduction

As requested by the EPA, DAS is providing comments on the Agency's preliminary human health risk assessment for chlorpyrifos. These comments are intended to address errors found in the EPA memorandum entitled "Chlorpyrifos: HED Preliminary Risk Assessment for the Reregistration Eligibility Decision (RED) Document. Chemical Number 059101. DP Barcode D257953" and the 16 Agency documents attached to said memorandum. In addition, DAS is submitting additional information to accompany this document for purposes of refining existing risk assessments as well as providing comments on differences of opinion in the interpretation of study results, including a recommendation for acute and chronic reference doses for use in conducting risk assessments, as well as revised dietary and occupational exposure assessments based on these recommended reference doses.

II. Comments on Errors, Uncited Studies, Omissions of Other Relevant Data, and Differences in Interpretation of Evidence in the HED Preliminary Risk Assessment and the Accompanying Attachments (16)

A. Hazard Identification, Endpoint Selection and FQPA Safety Factor

There are substantial differences in the approaches taken by the U.S. EPA and by DAS in the risk assessment of humans exposed to chlorpyrifos. These differences lead to marked differences in the resulting hazard assessment and are due to the Agency's use of default values when scientifically-valid studies show these defaults should be abandoned (Conolly et al., 1999; Dourson et al., 1996). For chlorpyrifos, and organophosphates in general, there is a wealth of valid scientific data that indicate many of these conservative defaults should be replaced. DAS feels there is sufficient valid data to replace conservative defaults with the following (details can be found in Appendix A):

- Scientifically valid human studies exist for chlorpyrifos. When such studies exist, they should take precedence over data from animal studies in setting RfDs for chlorpyrifos (Clegg and van

Gemert, 1999; Barnes and Dourson, 1988; Dourson and Stara, 1983; Boobis, 1998; Herrman, 1998).

- Human RBC AChE inhibition data should be used to set RfDs for chlorpyrifos. It is generally accepted that NOELs and RfDs used in a hazard assessment should be based on a measure of toxicity (e.g., cholinergic effects and/or AChE inhibition) and not on a measure of exposure (e.g., BuChE) (Lotti, 1995; Clegg and van Gemert, 1999; Chen, 1999; Carlock et al., 1999).
- When the same endpoint is considered, studies show a similar dose-response and NOELs for chlorpyrifos in humans, non-human primates, dogs, rats and mice. The animal studies strongly support that inhibition of human RBC AChE is the appropriate endpoint for chlorpyrifos hazard evaluation.
- There are sufficient data to conclude that the fetus and neonate are not more sensitive to chlorpyrifos than the adult. Two recent reviews of the relevant literature (Schardein and Scialli, 1999; Gibson et al., 1999) report the same conclusion.
- Acute and chronic RfDs proposed by DAS are consistent with those currently utilized by the WHO, the European Union and Canada (WHO, 1990). Acute RfDs, calculated from RBC AChE inhibition data from human studies were 0.05 mg/kg. Chronic RfDs calculated from RBC AChE inhibition data from human studies were 0.01 mg/kg/day. A recent, comprehensive analysis of the chlorpyrifos human and animal toxicity literature by a panel of toxicology and medical experts reached the same conclusions as above (Clegg and van Gemert, 1999).

1. <u>Comments Pertaining to the HED Preliminary Risk Assessment Document Dated July 23, 1999</u>

Page 4, line 30. Sentence is misleading. ChE refers to cholinesterase and represents a family of enzymes. DAS concurs that inhibition of AChE in the brain is the most sensitive “toxicological” effect of chlorpyrifos. However, butyrylcholinesterase (BuChE) and AChE in the RBC are inhibited by smaller dose levels of chlorpyrifos than required to inhibit brain AChE. Additionally, there is near unanimous agreement among the scientific and regulatory communities that inhibition

of BuChE and AChE in RBC are not toxicologically significant and should not be used as the basis of hazard evaluation.

Page 4, lines 32-33. The statement "Data from two human studies suggest humans may be more sensitive to plasma ChE inhibition than animals" is incorrect. This statement appears to be in error because the U.S. EPA failed to recognize that BuChE is much more sensitive to inhibition by chlorpyrifos than RBC AChE, and that BuChE is the primary enzyme in dog and human plasma while AChE is the major enzyme in rodent plasma. When these two facts are incorporated into the evaluation, it is evident that humans are no more sensitive to ChE inhibition than animals when the same endpoint is evaluated in each species. The NOEL for plasma ChE inhibition following daily administration of chlorpyrifos in the two species that have primarily BuChE in their plasma (i.e., dog and humans) is the same at 0.03 mg/kg/day. The NOEL for RBC AChE inhibition following daily administration of chlorpyrifos to the rat, dog and human are the same, 0.1 mg/kg/day. Clearly, humans are not more sensitive than animals to either BuChE or AChE inhibition, and they only appear to be more sensitive when different endpoints are compared.

Page 11, lines 18-21. Statement is misleading and leads to a flawed interpretation of the chlorpyrifos database. Species difference exists in whether BuChE or AChE is the primary cholinesterase found in the plasma. This difference is important because BuChE is much more sensitive than AChE to inhibition by chlorpyrifos. Thus, it is inappropriate to compare the NOEL for plasma cholinesterase inhibition in rats and humans because BuChE is the primary ChE in human plasma while over half of the ChE in rat plasma is AChE.

Page 13, line 24. Change eight to nine as all volunteers received nine daily oral doses of chlorpyrifos as noted in line 21, page 23 of this document.

Page 13, lines 23-25. The Agency's position that the "blurred vision, runny nose and a feeling of faintness" reported by one of four volunteers given nine daily doses of 0.1 mg/kg/day were cholinergic is inconsistent with the opinion of the physician, who was the study director and

treated this individual. This opinion was recently reviewed and confirmed by a panel of toxicology and medical experts (Clegg and van Gemert, 1999). In addition, tolerance develops to the muscarinic effects of organophosphates upon repeated administration. Thus, if this individual's symptoms were cholinergic they should have been observed after the first or second day's dose, not after the ninth daily dose. Additionally, data from a new human study documents that a single oral dose, which exceeds by over a factor of two the total amount of chlorpyrifos given in nine days in Coulston et al. (1972), did not cause any cholinergic effects in 12 human volunteers (Kisicki et al., 1999).

Page 13, lines 41-42. The statement that plasma and RBC ChE were inhibited in volunteers given the 5 mg/kg dermal dose is incorrect. There was no change in either plasma or RBC ChE in volunteers given the dermal 5 mg/kg dose. Plasma and RBC ChE levels were measured repeatedly in this study, and it is essential to look at the time-course for changes in plasma and RBC ChE and at the kinetic data. The plasma ChE measurements following the dermal dose exhibited large fluctuations in both directions which were not biologically plausible. The Agency has interpreted the lower plasma and RBC ChE measurements three and four days post-exposure as due to treatment by ignoring the kinetic data, which show blood chlorpyrifos levels would have peaked at least two days before this, and that the quantity of chlorpyrifos absorbed was insufficient to inhibit either plasma nor RBC ChE. If all of the data from this study is considered, the obvious conclusion is that neither plasma nor RBC ChE were depressed in volunteers given the 5 mg/kg dermal dose of chlorpyrifos.

Page 14, lines 8-17. This paragraph is in error as it fails to recognize that ChE activity in the plasma of humans and rats is due to a different enzyme and that the principal enzyme found in human plasma (BuChE) is much more sensitive to inhibition by chlorpyrifos than that in rat plasma (AChE). If the NOELs for plasma ChE inhibition following repeated administration of chlorpyrifos are compared in two species where BuChE is the primary enzyme, i.e., man and dog, the NOELs are the same, 0.03 mg/kg/day. If the NOELs for AChE inhibition in the blood, i.e., human and dog RBC and rat plasma and RBC, following repeated administrations of chlorpyrifos

are compared, the NOELs are identical 0.1 mg/kg/day. It is impossible to use plasma ChE inhibition to determine if humans are more sensitive than rats because one is not comparing the same endpoint. The conclusion that the symptoms reported by one individual in the high dose group in the Coulston et al. (1972) study were cholinergic is in conflict with those of the study director; who was a medical doctor, treated this individual, and was aware a ChE agent had been given, and what the signs and symptoms of cholinergic toxicity are. Moreover, the study director's interpretation of these symptoms is corroborated by a subsequent study. In this study (Kisicki et al., 1999) no treatment-related signs or symptoms were observed in 12 volunteers given a single oral dose of chlorpyrifos that exceed by more than twice the total amount of chlorpyrifos administered in the top dose in nine days of the Coulston study.

Page 14, lines 28-30. The sentence "*The HIARC concluded that there is sufficient evidence in the scientific literature to conclude that exposure to chlorpyrifos results in increased susceptibility to neonates as compared to adult rats*" is not consistent with the conclusion of the open literature as stated in the Toxicology Chapter for Chlorpyrifos, May 6, 1999, which states on page 26, lines 13-17:

> "*In summary, neonatal rats were shown to be much more sensitive to acute doses of Chlorpyrifos at levels near the maximum tolerated dose than are adult rats, as measured by lethality (LD10 values). However, measurement of neurobiochemical and/or neurobehavioral endpoints demonstrated that when Chlorpyrifos was administered during gestation, maternal rats were more sensitive to Chlorpyrifos exposure than were their fetuses or neonates, and when Chlorpyrifos was administered postnatally, adult rats were more sensitive than neonatal or weanling rats.*"

The registrant concurs with the above citation and a statement made in the report of the FQPA Safety Factor Committee of April 5, 1999, which clearly states that the Agency's concerns are for:

"*sensitivity to neurochemical and/or neurobehavioral changes following repeated, low-dose exposure should be of more concern for risk assessment and regulatory decisions making, especially in light of the FQPA.*"

These two statements clearly indicate that the fetus, infants and children would not be expected to be more sensitive to chlorpyrifos following repeated low-dose exposures.

Page 16, Table 1. Data in this table are from pre-GLP studies and should be replaced by the data from more recent studies.

Table 1. Acute Toxicity Results for Technical Chlorpyrifos

STUDY	MRID Number	RESULTS	CATEGORY
Acute Oral LD_{50} - rat	44209101	223 mg/kg M & F	II
Acute Dermal LD_{50} - rabbits	44209102	>5000 mg/kg	IV
Acute Inhalation LC_{50}; rat Supplementary	00146507	LC_{50} >0.2 mg/L (200 mg/m^3) (nominal concentration)	II
Eye Irritation - rabbit	44209103	slight irritation resolved within 24 hr	IV
Dermal Irritation - rabbit	44209104	Irritation resolved within 7 days	III
Dermal Sensitization - guinea pig	44209105	non-sensitizing	NA
Acute Delayed Neurotoxicity in hens	00097144 00405106	not neurotoxic at 50, 100 or 110 mg/kg	NA

Page 16, lines 11-12. Statement is inconsistent with the FQPA legislation. There is no provision in the FQPA legislation for retaining an FQPA safety factor because of concern of the wide use of a pesticide or potential for exposures to infants and children.

Page 16, lines 13-15. Statement is inaccurate and misleading. The effects observed in the offspring of dams given the 5 mg/kg/day dose level were secondary to altered maternal care. That the consequence of maternal neglect in rodents is more apparent and severe in the dependent neonate than the effects of the chlorpyrifos in the dam is not evidence of increased neonatal sensitivity.

Page 16, line 16 through page 17, line 1. Statement is inaccurate and misleading. There are data from lower dose levels which show the increased neonatal sensitivity reported in the cited paper by Moser and Padilla is a high dose phenomenon that does not occur at "lower, real world exposure to chlorpyrifos in the diet" which the Agency states "are of more concern for risk assessment and regulatory decisions." Additionally, this statement is inconsistent with subsequent statements made by the Agency:

> "*The toxicology database is complete for assessing the effects of chlorpyrifos following in utero and/or postnatal exposure;*" (Chlorpyrifos – Report of the FQPA Safety Factor Committee. 05-APR-1999, p 6, lines 21 - 22)

or:

> "*The data submitted to the Agency under Subdivision F Guidelines provided no indication of increased susceptibility to in utero exposure in developmental toxicity studies and/or to pre- and post-natal exposure in reproduction studies with chlorpyrifos;*" (Chlorpyrifos – Report of the FQPA Safety Factor Committee. 05-APR-1999, p 6, lines 23-26)

Thus, there are sufficient data from a developmental neurotoxicity study, a developmental kinetcs/cholinesterase inhibition study, a multi-generation reproduction study, and the published literature to determine that the neonate/infant is not more sensitive than the adult following single or repeated administration at dose levels that are relevant for risk assessment and regulatory decision making.

Page 17, lines 34-35. The decision to apply an FQPA safety factor of 3x to chlorpyrifos is inconsistent with pertinent legislation and the Agency's own analysis of the data for chlorpyrifos as demonstrated by the following citations which were taken from page 17:

- "*...most significant exposures to chlorpyrifos are well characterized…*
- "*the toxicity data base is complete*"
- "*…no indication of increased susceptibility to in utero exposure …and/or to*
- "*…no quantitative evidence of increased susceptibility in the developmental neurotoxicity study…*"
- "*…qualitative evidence of increased susceptibility … was only observed at the*
- "*…difference in sensitivity was observed at very high doses … which were the only dose level tested.*"

2. Comments Pertaining to the Toxicology Chapter for Chlorpyrifos Dated May 6, 1999

Page 2, Table 1. Data in the table for technical chlorpyrifos are from pre-GLP studies and should be replaced by the data from more recent acute toxicity studies as previously mentioned.

Page 3, lines 4-5. The sentence "*The most sensitive toxicological endpoint following subchronic oral exposure is inhibition of plasma and red blood cell cholinesterase in dogs at 0.22 mg/kg/day (Barker, 1989) and plasma inhibition in rats at doses as low as 0.025 mg/kg/day (Crown et al., 1985)*" is incorrect and misleading. The registrant agrees ChE inhibition is the most sensitive effect due to exposure to chlorpyrifos. However, there is near unanimous scientific and regulatory agreement that inhibition of plasma and RBC ChE activity are not toxic effects. The document also incorrectly states that the lowest observed effect level (LOEL) for plasma ChE inhibition in the dog is 0.22 mg/kg/day. In doing so, the Agency has ignored data from the chronic dog study (MRID 00146519), which demonstrate that plasma ChE activity was decreased by 40% nine days after dogs were started on a diet providing 0.1 mg/kg/day. Plasma ChE activity was also lower at this interval in dogs given diets providing 0.03 mg/kg/day, although the mean activity was within 20% of the control. This same study also demonstrated that the NOEL for

RBC ChE inhibition following repeated administration of chlorpyrifos to the dog is 0.1 mg/kg/day.

Page 3, lines 5-8. The sentence "*Rats exposed to higher doses also exhibited increased brain and heart weight, adrenal gland effects and decreased body weight gain at 1 mg/kg/day and hematological alterations suggestive of anemia at higher doses of 10 mg/kg/day (Szabo et al., 1988)*" is incorrect. In Szabo et al. (1988), decreased body weight was observed only at the top-dose level tested of 15 mg/kg/day. There was no 10 mg/kg/day dose level in this study. Changes in brain and heart weight were observed only at this high dose level and were considered secondary to the decreased body weight. No adrenal effects were observed in rats given the 1 mg/kg/day dose level. It is the opinion of EPA reviewers, not the study authors', that the minor decrease in RBC and platelets were suggestive of anemia. The speculation of the EPA reviewer that the hematological alterations are suggestive of anemia is not supported by any data from this or any other study.

Page 5, lines 3-6. The sentence "*In all animal species, the most sensitive toxicological endpoint is inhibition of plasma, red blood cell and brain cholinesterase that occurred at levels in the range of 0.03 to 1 mg/kg/day*" is inaccurate and misleading. The registrant agrees that ChE inhibition is the most sensitive effect of exposure to chlorpyrifos. But there are marked differences in the NOEL for plasma, RBC and brain ChE inhibition that are species dependent. The NOELs for plasma and RBC ChE inhibition in the dog are 0.03 and 0.1 mg/kg/day, respectively. The NOEL for plasma and RBC ChE inhibition in the rat are both 0.1 mg/kg/day. The NOEL for brain ChE inhibition in both species is 1.0 mg/kg/day.

Page 5, lines 6-8. The sentence "*Dogs appear to be the most sensitive species for cholinesterase inhibition and systemic effects, as noted by increased liver weights in dogs exposed to 3 mg/kg/day*" is inaccurate and misleading. The NOELs for plasma ChE inhibition following repeated administration of chlorpyrifos is the same in the dog and man, the two species where plasma ChE activity is due primarily to BuChE. The NOELs for RBC AChE inhibition following

repeated administration of chlorpyrifos is the same in the dog, rat and human (i.e., 0.1 mg/kg/day). Furthermore, it is misleading for the Agency to imply that one species is more sensitive than another based on an effect (increased liver weight) it considers an adaptive response (see Table 3).

Page 5, lines 10-11. The basis for the statement "Mice appear to be the least sensitive," should be provided. It should also be noted that the degree of plasma, RBC and brain ChE inhibition following repeated doses of chlorpyrifos to rats (Szabo et al., 1988) and mice (Davies et al., 1985) are nearly identical.

Page 8, lines 7-9. The sentence "*At higher levels of 5 mg/kg/day, the pups exhibited decreased body weight/body weight gain and food consumption in both sexes, reductions in pup viability, delays in development, decreased brain weight and morphometric alterations in the brain*" is misleading and should be modified as follows: "At higher levels of 5 mg/kg/day, the pups exhibited the following effects the study director attributed to maternal neglect: decreased body weight/body weight gain and food consumption in both sexes, reductions in pup viability, delays in development, decreased brain weight and morphometric alterations in the brain."

Page 8, lines 9-11: The sentence "*However, these effects were observed in the presence of maternal toxicity as evidenced by fasciculations, hyperpnea and hyperactivity*" is incomplete and should be modified as follows: "However, the effects in pups were observed only at a dose level that caused a significant decrease in maternal body weight gain on gestational days 17-20 and post-natal days 0-3, and also caused clinical signs of cholinergic toxicity in the dam as evidenced by fasciculations, hyperpnea and hyperactivity."

Page 10, lines 1- 2. This sentence is inaccurate as it fails to indicate that possible evidence of reproductive toxicity was observed in only one of two generations of rats.

Page 10, lines 2-5. This sentence is inaccurate as it fails to report that P1 females gained less weight on lactation days 1 through 21. In addition to the decreased maternal body weight gain at this dose level, there was an increased incidence of weak thin pups and no milk was found in the stomach of the pups that died. These observations indicate the reproductive effects observed at this dose level were secondary to maternal neglect.

Page 11, lines 20-23. Sentence is misleading as it implies the cited paper (Capodicasa et al., 1991) expresses concern chlorpyrifos may produce organophosphate-induced delayed neuropathy (OPIDN) while the authors clearly state, "It is likely that delayed polyneuropathy would develop in both species only after severe cholinergic toxicity requiring aggressive antidotal treatment."

Page 11, entire paragraph. If this document is intended to provide the best information on the potential of chlorpyrifos to inhibit neurotoxic esterase (NTE), it is unfortunate that the paper by Richardson et al. (1993) was not mentioned. This paper extends the observation of Capodicasa et al. (1991) and shows that repeated doses of chlorpyrifos are unable to cause sufficient inhibition of NTE to cause OPIDN.

Page 14, lines 1-2. The sentence "*Neurotoxic effects consisted of decreased motor activity on day 1 through 8 (females only)*" is incorrect and misleading. Changes in motor activity can be due to many things other than neurotoxicity and there is no mention of what dose level at which this was observed. The sentence should therefore be modified as follows: "Decreased motor activity was observed following the 50 and 100 mg/kg dose level on day 1 (both sexes) and day 8 (females only)."

Page 14, lines 5-6. The sentence "*Grip performance on day 1 revealed a possible treatment-related decrease with increasing dose.*" is inaccurate and should be modified as follows: "Grip performance was decreased only on day 1 in animals given the 50 and 100 mg/kg dose level, but did not exhibit a dose response."

There were no significant effects on bodyweight, food consumption, or pregnancy parameters" is inaccurate and misleading. While body weight was not statistically different over the entire study, body weight gain was significantly lower in dams given the high dose level of 5 mg/kg/day on gestation days 17-20 and lactation days 0-3. This is important because it coincides with the interval when increased pup mortality and decreased weight gain were observed, and supports the authors' conclusion that the effects on the pups were secondary to maternal toxicity and altered care.

Page 17, lines 13-24. Description of the pup body weight data is misleading as it obscures the fact that pup body weight gain for the high-dose group was lower than controls only the first few days after birth. This is the interval during which the dams exhibited clinical cholinergic signs and depressed weight gain. The high-dose pup body weight remained depressed at later intervals; however, the body weight gain at these later intervals was comparable to that of the controls.

Page 18, line 23. Guidance provided by the EPA (Makaris et al., 1998) indicates that the effects observed in the high-dose pups should not be classified as neurotoxicity. This document states that one of the criteria used to determine if a developmental neurotoxicity study is required is if a

substance had been shown to “affect brain weight in offspring, which does not appear to be related solely to general growth retardation, following pre- and/or postnatal exposure.” Thus, the Agency recognizes that decreased brain weight in offspring *per se* is not evidence of neurotoxicity and that retarded growth leads to decreased brain size. One of the supplements to the developmental neurotoxicity study which the Agency is reviewing (MRID 4478301) documents that the pup brain weights in this study were in proportion to body size in all dose groups. When the Agency reviews this supplement DAS expects their evaluation of this study will be appropriately modified.

Page 19, line 11. Change “declined to 87%” to “declined by 87%.”

Page 19, line 34. Delete “essentially” as TCP was not detectable in the blood of low- and mid-dose pups on lactation day 5.

Page 20, line 3. Add “24 hrs after the last dose” to end of this sentence. The specimens collected on previous days were collected four hours post-dosing.

Page 20, line 4. Change “had inhibition of brain ChE to 87.8–93.1%” to “had brain ChE levels of

Page 20, line 7. Add “24 hrs after the last dose” to end of this sentence. The specimens collected on previous days were collected four hours post-dosing.

Page 20, line 8. Change “plasma ChE had recovered but RBC activity remained inhibited at 53.6% of the control level” to “plasma ChE had returned to control level, but RBC activity was still only 53.6% of the control level.”

Page 20, line 10. Change “22.3” to “23.3.”

Page 20, line 11. Change “remained inhibited at” to “was still only.”

Page 20, line 14. Change “day 11 and were similar to controls on lactation day 22” to “day 11 (24 hrs after the last dose) and were similar to controls on lactation day 22 (12 days after the last dose).”

Page 20, line 20. Delete “inhibited.”

Page 21, lines 11-13. Note in this sentence that it is the EPA that believes this individual’s symptoms were cholinergic. The study director (who is a medical doctor, treated this individual, and was aware a ChE agent had been given and was knowledgeable about the signs and symptoms of cholinergic toxicity) did not consider these to be cholinergic in nature. This opinion was recently reviewed and confirmed by a panel of toxicology and medical experts (Clegg and van Gemert, 1999).

Page 21, lines 19-22. The Agency needs to explain why it feels a study designed to evaluate the dose response for ChE inhibition and cholinergic effects needed “to control this study for confounding factors such as smoking.” There is nothing in the literature to show that any of the standard confounding factors studies of this type control have any impact on either the dose response for ChE inhibition or cholinergic effects.

Page 21, lines 22-23. Note that it is the study director (who is a medical doctor, treated this individual, and was aware a ChE agent had been given and was knowledgeable about the signs and symptoms of cholinergic toxicity) who did not consider these symptoms to be cholinergic in nature. The study director’s interpretation that these symptoms were not cholinergic is consistent with subsequent studies which show a single dose that is greater than twice the total quantity of chlorpyrifos administered over nine days in the Coulston study did not cause any treatment related clinical effects.

Page 21, line 30. A blood specimen was not collected one hour post-dosing from the main group of volunteers.

Page 21, line 31. Insert "up to" prior to "9 days (dermal)."

Page 21, lines 35-36. The phrase that "peak RBC inhibition of 11 – 52 % on day 4." is incorrect. The RBC data exhibited large fluctuations which were biologically implausible. The Agency's assertion that RBC ChE was decreased four days post-dosing is in conflict with the kinetic data, which demonstrate that absorption of chlorpyrifos was complete within 24 hours post-dosing and that plasma esterase activity was returning to baseline within 24-48 hours post-dosing. If sufficient chlorpyrifos had been available on day 3 and 4 to inhibit RBC ChE activity, plasma ChE would have continued to decline, when in fact it was increasing.

Page 21, lines 35-37. The statement that "*Men dermally exposed to 5 mg/kg chlorpyrifos exhibited peak plasma ChE inhibition of 27-45% on day 3, and mean RBC ChE inhibition of 8.6% on day 4*" is in error. Seven of the 10 times plasma ChE was measured following the 5 mg/kg dermal dose, mean plasma ChE activity was greater than plasma ChE measured immediately prior to dosing. One time the mean plasma ChE level was essentially the same as the pre-exposure level, i.e., 1.12 versus 1.11, and twice the mean plasma ChE activity was lower than the pre-exposure measurement. However, in both these instances, the change from the preceding and following measurements were not biologically plausible. The fluctuations in RBC ChE activity were smaller than for plasma ChE activity and did not exhibit a biologically plausible pattern. Clearly, the lower plasma and RBC ChE values cited by the Agency are artifacts and not due to exposure to chlorpyrifos.

Page 23, lines 2, 3. Identify the dose level being discussed and change 15% to 16%.

Page 23, lines 3-5. The sentences "*The decrease in activity of rats treated with 50 or 100 mg/kg began within 10 minutes of treatment. By 12 hours after treatment, both groups were*

approximately 11% of the control group and had not shown signs of recovery" are inaccurate, misleading, and need to be modified. In both sentences it should be specified that it is plasma ChE activity being discussed. This should also be made clear in the last phrase "had not shown signs of recovery," which implies toxicity was observed when the observation actually was a small decrease in plasma ChE activity.

Page 23, line 23. Delete "reportedly." Using this adjective for only one observation, when it in fact applies to all data in this document, implies the Agency disagrees. Moreover, the section in parenthesis should read "(*in vitro* half life in rat blood of 10 sec and 55 sec in human blood; Brzak et al., 1997)."

Page 25, lines 16-18. The Agency should explain how it reached the conclusion that the correlation between brain and plasma ChE inhibition reported by Pope et al. should be considered substantive. It appears that the Agency has selected only those studies which supports its preconceived position. The selected studies used massive dose levels and a route of administration inappropriate for hazard evaluation. One of the cited papers even noted "*that while plasma cholinesterase levels, under defined experimental conditions, may provide a quantitative estimate of the extent of cholinesterase inhibition in the central nervous system following organophosphate exposure, factors such as route of exposure and time after treatment when cholinesterase is assayed could influence the degree of correlation.*" The Agency needs to explain why it ignored the numerous studies that used routes and dose levels appropriate for risk assessment and which demonstrate that plasma and RBC ChE inhibition occur at much lower dose levels than brain AChE inhibition.

Page 25, lines 19-26. Summary misrepresents data. In the cited study huge doses were administered which caused massive inhibition of ChE in all compartments. Since chlorpyrifos inhibited ChE in all compartments it is not surprising that a correlation could be found. However, inspection of the data from the lowest dose level tested (30 mg/kg) provides clear evidence that plasma and RBC ChE are much more sensitive to inhibition than brain ChE. Moreover, studies

conducted which used routes of administration and dose levels that are appropriate for risk assessment demonstrate that plasma and blood ChE activity are much more sensitive to inhibition than brain ChE, and that the correlation between brain and plasma ChE inhibition is an artifact of the high dose levels used.

Page 25, lines 22-32. The Agency should explain why it gives preference to animal studies which used massive doses and routes of administration inappropriate for risk assessment when it has data from animal and human studies which utilized dose levels and routes of administration appropriate for risk assessment. This is particularly disturbing because the studies conducted using dose levels and routes of administration appropriate for risk assessment consistently demonstrate that plasma and RBC ChE are much more sensitive to inhibition than brain ChE.

Page 25, lines 33-34. Change "was reportedly inhibited at a lower dose than the erythrocyte cholinesterase activity" to read "was inhibited at a lower dose than the erythrocyte cholinesterase activity." The data clearly demonstrate that plasma was inhibited by lower dose levels than RBC ChE. Additionally, the greater sensitivity of plasma versus RBC ChE to inhibition by chlorpyrifos was observed in a subsequent study (Nolan et al., 1984) and in individuals who are involved in the manufacture of chlorpyrifos (Brenner et al., 1989; Burns et al., 1998).

Page 25, lines 34-37. The statement "*We have no explanation for this reversal of effect with respect to plasma and erythrocyte cholinesterase responses except that it may have to do with inherent differences between human and rat, or the circumstance of exposure*" is difficult to understand. The Agency is aware that ChE activity in the plasma of humans and dogs is almost entirely due to BuChE, while in rodents the principal enzyme in the plasma is AChE. BuChE is much more sensitive to inhibition than AChE (Amitai et al., 1998); thus, the explanation for the greater sensitive of BuChE (plasma) versus AChE (RBC) to inhibition in humans is well explained. Whether the reason for this difference is understood is of little regulatory importance, however. There is no question that it is real, as it has been demonstrated repeatedly in other studies (Nolan et al., 1984; Brenner et al., 1989; Burns et al., 1998).

Page 25, lines 37-38. It is an error for the Agency to attribute the greater inhibition of plasma versus RBC ChE activity in the Coulston et al. (1972) study to "The limited number of subjects and variability of the cholinesterase assay methodology." First, the degree of plasma ChE inhibition was much greater than the variability. Second, the Agency has data from several other studies involving humans (Nolan et al., 1984; Brenner et al., 1989; Burns et al., 1998), all of which demonstrate that human plasma ChE activity is much more sensitive to inhibition than RBC ChE activity. Thus, the greater sensitivity of human plasma versus RBC ChE activity to inhibition by chlorpyrifos has been observed in a large number of individuals, and the fact that it is repeatable makes any argument about variability in the assay moot.

Page 26, lines 1-2. The statement "*there is no reason to conclude that brain cholinesterase inhibition in the human case study would not be a correlate of plasma cholinesterase inhibition*" ignores what is known about the biology of ChE and chlorpyrifos. Cholinesterase activity in the plasma of humans and dogs is primarily BuChE. BuChE is a different enzyme than the enzyme responsible for ChE activity in the brain and RBC, which is AChE in all species. BuChE is much more sensitive to inhibition by chlorpyrifos than AChE. Chlorpyrifos, *per se*, is a weak inhibitor of BuChE and AChE, and must be activated in the liver by oxon. The oxon is transported from the liver to its site of action. Thus, the potential for chlorpyrifos to inhibit ChE activity depends on the sensitivity of the enzyme being inhibited and distance of the enzyme from the liver. Because ChE activity in the plasma of humans and rats are due to a different enzyme, it is inappropriate to extrapolate data on rodent plasma to humans. However, because ChE activity in the RBC and brain of humans and rats is due to the same enzyme (AChE), it is appropriate to base conclusions about the relative sensitivity of AChE in the RBC and brain of humans on rodent data. These data consistently show that the NOEL for brain AChE inhibition is 10 times greater than the NOEL for RBC AChE inhibition.

3. Comments Pertaining to the Report of the FQPA Safety Factor Committee Dated April 5, 1999

Page 2, lines 17–19. The following sentence is inaccurate and misleading. "*Qualitatively, however, there was evidence of increased susceptibility at the high dose (5 mg/kg/day) based on the concern for the severity of effects seen in the dams and pups*." The effects observed in the offspring were secondary to decreased maternal care and have been observed following maternal neglect caused by other agents (Kai et al., 1984; Baroncelli et al., 1995). The consequence of maternal neglect in rodents is more apparent and severe in the dependent neonate than the effects of the chemical on the dam. However, it is inappropriate to interpret the effects of maternal neglect on the rodent neonate as evidence of increased sensitivity of the human infant.

Page 2, lines 26–36. This section is incomplete. None of the studies conducted at lower dose levels or repeated administration were reviewed. The registrant acknowledges that pups have greater ChE inhibition than adults following a large single bolus dose, which is many multiples of the NOEL. This difference is also apparent in pups given even higher dose levels which cause clinical signs and mortality. However, pesticides are regulated on NOELs and LOELs, not on what is observed at near lethal dose levels. Moreover, the Agency specifically states:

> "*Sensitivity to neurochemical and/or neurobehavioral changes following repeated, low-dose exposure should be of more concern for risk assessment and regulatory decisions making, especially in light of the FQPA*." (Page 3, lines 3– 6)

The failure of the EPA to review the studies conducted at lower dose levels and repeated administration (Chakraborti et al., 1993; Pope and Liu, 1997; Liu et al., 1999) is puzzling. These studies, which were not reviewed, demonstrate the dose response curve for chlorpyrifos is appreciably steeper in neonatal rats than adults, and these curves cross at about 1 mg/kg/day, which is a NOAEL for brain AChE inhibition in both the neonate and adult. Additionally, these studies demonstrate that the neonate is not more sensitive than the adult following repeated administration of chlorpyrifos.

Page 3, lines 1–10. This section is inaccurate. There are data from a developmental neurotoxicity study, a multi-generation reproduction study, and the published literature which demonstrate that the neonate is not more sensitive than the adult following lower dose levels or upon repeated administration. The Agency states that it is "lower, real world exposure" to chlorpyrifos "that should be of more concern for risk assessment and regulatory decisions." Moreover, none of the numerous studies in the published literature, which show the neonate is not more sensitive at lower dose levels (e.g., Pope and Lui, 1997), or upon repeated administration (Chakraborti et al., 1993; Liu et al., 1999) were reviewed in the previous section and appear to have been omitted by the EPA when the "weight of the evidence" was considered. Inclusion of these studies consideration of in the weight of evidence demonstrate the infant is not more sensitive than the adult following either single or repeated administration of chlorpyrifos at dose levels likely to be encountered.

Page 6, lines 4-5. Statement is inconsistent with the FQPA legislation. There are no provisions in the FQPA legislation for retaining an FQPA safety factor because of concern of the wide use of a pesticide or potential for exposures to infants and children.

Page 6, lines 6–8. Statement is inaccurate and misleading. The effects observed in the offspring of dams given the 5 mg/kg/day dose level were secondary to altered maternal care (Hoberman et al., 1999; Schardein and Scialli, 1999). The consequence of maternal neglect in rodents is more apparent and severe in the dependent neonate than the effects of the chlorpyrifos in the dam. However, this is not evidence of increased neonatal sensitivity.

Page 6, lines 9–11. Statement is inaccurate and misleading. There are data from lower dose levels which show the increased neonatal sensitivity reported by Moser and Padilla is a high-dose phenomenon. These studies show the neonate is not more sensitive to chlorpyrifos than the adult following "*lower, real world exposures*" that the Agency states are of "*more concern for risk assessment and regulatory decisions*." Additionally, this statement is inconsistent with subsequent statements made by the Agency:

> "*The toxicology database is complete for assessing the effects of chlorpyrifos following in utero and/or postnatal exposure*;" (page 6, lines 21-22)

and

> "*The data submitted to the Agency under Subdivision F Guidelines provided no indication of increased susceptibility to in utero exposure in developmental toxicity studies and/or to pre- and post-natal exposure in reproduction studies with chlorpyrifos*;" (page 6, lines 23–26)

Thus, there are sufficient data from a developmental neurotoxicity study, a developmental kinetics/cholinesterase inhibition study, a multi-generation reproduction study, and the published literature to determine the neonate/infant is not more sensitive than the adult following single or repeated administration of chlorpyrifos at dose levels that are relevant for risk assessment and regulatory making decisions, especially in light of FQPA.

Page 7, lines 1-3. This statement is inconsistent with the database and the EPA guidance documents. The EPA has all the studies it identified as needed to make a decision relative to removal of the FQPA safety factor. These studies provide no evidence of increased susceptibility of the neonate to chlorpyrifos. There are no provisions in the FQPA legislation to retain the FQPA safety factor because of widespread use.

B. Dietary Exposure and Risk Assessment

1. Comments Pertaining to the Acute Dietary Risk Assessment for Chlorpyrifos Document Dated July 22, 1999

The Agency has incorporated significant refinements into the acute dietary risk assessment. DAS commends the Agency for continuing to work toward producing realistic acute dietary assessments. Although DAS agrees with many of the approaches and methods used, further refinements, such as use of actual monitoring data for cranberries and recognition of the potential reduction in residues from cooking, etc., are needed to produce a truly realistic assessment. In

addition, several aspects of the assessment procedures, such as construction of the residue distribution files and the estimates of the limit of detection (LOD), are still developing policies within the Agency. At the present time, DAS cannot verify the accuracy of these distribution files for comment.

The EPA presents the results obtained at the 99.9th percentile. DAS does not believe that the 99.9th percentile estimates, as they are currently derived, are scientifically sound or representative. The inherent limitations associated with calculations at this extreme percentile have been shown to overestimate exposures and, therefore, the results may be in error. DAS encourages the Agency to consider results over a range of percentiles such as 95 to 97.5% as more realistic and scientifically valid.

At this time, acute dietary exposure at the 99.9th percentile to chlorpyrifos is less than 50% of the EPA's proposed RfD and less than 5% of the RfD proposed by DAS for the highest exposed population when default values for cranberries are removed. At the 95th percentile, acute dietary exposure to chlorpyrifos is less than 10% of the EPA's proposed RfD and less than 1% of DAS's proposed RfD for the highest exposed population when default field values for cranberries are removed.

Page 2. "*The distinguishing factor between a Tier 3 and Tier 4 assessment is the inclusion of market basket survey data. For purposes of this risk assessment, the exposure assessment termed "Tier 3/4" includes some market basket data (only for beef and pork), whereas the "Tier 4" assessment includes all available market basket data (total of 9 commodities).*"

Page 2. "*The NFS data supplied by Dow represent are now somewhat dated as compared to PDP and FDA data (samples were collected in 1993) and are limited (200 samples for most commodities). For some commodities included in the NFS, more recent and extensive data are available from monitoring programs. For example, the NFS included 200 apple samples, but PDP collected 1908 samples from 1994-1997 and FDA collected 1342 samples from 1992-1997. Because of the limited and dated (relative to PDP and FDA monitoring data) NFS data, the Agency elected to conduct a Tier 3/4 analysis, which only incorporated NFS data for beef and pork, because those are the best data available for meat.*"

Page 9. "*The dietary exposure analyses relied primarily on monitoring data obtained either "at the farm gate" in the case of FDA or in regional distribution warehouses for PDP data. The NFS results are for samples obtained at supermarkets, but only represent one year of data. Roadside produce stands, farmer's markets and similar outlets are not represented in the analyses.*"

Page 10. "*The NFS data supplied by Dow are now somewhat dated (samples were collected in 1993) in comparison to more recent PDP and FDA data, and are limited (200 samples). For some commodities included in the NFS, more recent and extensive data are available from monitoring programs. For example, the NFS included 200 apple samples, but PDP collected 1908 samples from 1994-1997 and FDA collected 1342 samples from 1992-1997. Because of the limited and dated NFS data, the Agency elected to conduct a Tier 3/4 analysis, which only incorporated NFS data for beef and pork, because those are the best data available for meat.*"

DAS supports the use of the Tier 4 assessment as the best understanding (to date) of exposure of the population to chlorpyrifos. Collection of samples in 1993 renders the data comparable to both FDA and USDA Pesticide Data Program (PDP) data because the FDA samples reported in 1992 are a summary of samples actually collected in 1991; likewise, samples collected by PDP in 1994 are a summary of samples collected in 1993. Furthermore, product use patterns have not changed significantly since 1993; therefore, the magnitude of residues detected in subsequent years is not expected to increase. Also, percent market share from Biological & Economics Assessment Division (BEAD) estimates have decreased so the frequency of detection would not be expected to increase. The number of samples collected for the marketbasket survey is also sufficient as a minimum sample size was determined using statistically validated procedures as published by Bolles et al. (*J. Agric. Food Chem*, 1999). In Appendix B, a graph is shown comparing the similarity of the marketbasket data submitted by DAS and the PDP monitoring data for 1996. The similarity between the data validates both the PDP monitoring data and the marketbasket data as measurements of residues encountered by consumers prior to food preparation. Additionally, "Supermarkets were the only type of grocery outlet sampled because many of the target food items were not available in convenience stores" (*J. Agric. Food Chem*, 1999).

The Tier 4 assessment is a better estimate of exposure to chlorpyrifos based on scientifically valid data from the marketbasket survey data submitted by DAS.

Page 3. "*HED is also performing a critical exposure contribution analysis to determine if there was any individual with excessive consumption patterns that would affect the risk estimates. This analysis has not been completed.*"

DAS encourages HED to determine if any individual with excessive consumption patterns would affect the exposure analysis. Previous work with acute dietary assessments for chlorpyrifos have indicated the results at the 99.9th percentile are driven by extreme and even questionable consumption patterns, such as a three-year-old child who consumes 100 g of lemon juice concentrate and a three-year-old eating 356 g of boiled cabbage, all in one day (Oliver, 1999). DAS would like to work with HED to examine this issue during the next comment period, allowing more time for evaluation.

Page 4. "*Chlorpyrifos has tolerances on a large number of commodities, there are over 100 tolerances in 40 CFR 180.342. Tolerances for chlorpyrifos are being reassessed as part of reregistration. In particular, the metabolite 3,5,6-trichloro-2-pyridinol (TCP) will be removed from the tolerance expression, and only parent chlorpyrifos will remain.*"

DAS agrees it is appropriate to base the tolerances on chlorpyrifos only. Based on the tolerances, DAS recommends removal of popcorn, garlic, beets, and beet greens from the assessment because no crop tolerances exist for these raw agricultural commodities.

Page 5. "*Recently, agency statisticians have developed a method using standard statistical procedures to adjust the composited residues to reflect residues that could be present, potentially, in single-serving sizes of commodities. The methodology assumes the following: 1) the weight of the sample that was composited based on PDP Standard Operating Procedures on the amount of sample collected, 2) the number of units (such as apples or oranges) in the sample that was composited, and 3) the distribution of residues in the units is lognormal. There are some data to justify the use of assumption #3. This method yields a distribution of theoretical single-serving residues (based on the composited residues) that would have resulted if the residue analysis had been done on single-serving items without compositing. Currently, this method is being applied to several of the acute dietary assessments for the first 9 organophosphates (OPs), but will require additional peer review and validation before it can be used routinely in acute dietary assessments.*"

Consideration of the various methods for decompositing PDP monitoring and marketbasket data should be reviewed prior to finalization of the acute dietary risk assessment for chlorpyrifos. The SAP supported this opinion at its meeting in May 1999: "Even though the Panel did not have the opportunity to critically review the information, the Panel recommends that Dr. Sielken publish the procedure and examples of its implementation in a peer-reviewed journal. Following this, the Agency should actively explore the feasibility of using it or adapting it for the exposure estimation problems that were the focus of the session." (SAP Report No. 99-03; May 25, 1999). Clearly, a method for decompositing monitoring data has not been finalized. Until the most scientifically valid method has been recognized and approved, acute dietary risk assessments using decomposited data should not be considered final.

Page 7. "*HED is also aware that the Cranberry Institute has access to monitoring data for cranberries. If these data are submitted to the Agency and validated, they may be used to further refine exposure estimates.*"

DAS is also aware the Cranberry Institute has access to monitoring data for cranberries; however, DAS has not received the data in a timeframe that would allow incorporation of the data into a risk assessment for purposes of this response. DAS has completed a risk assessment using the Tier 4 assessment conducted by HED as a baseline and compared the results to the same assessment removing residues measured in field trials for cranberries as a source of exposure. In other words, zeros have been entered for cranberries. The results are summarized in the following two tables:

EPA Baseline Assessment <u>with</u> Cranberries

Population	Percent RfD (RfD = 0.0017 mg/kg/day)		
	95th Percentile	99th Percentile	99.9th Percentile
US	4	10	44
All Infants	8	15	43
Nursing Infants	3	9	58
Non-Nursing Infants	9	16	43
Children (1-6 years)	8	18	120

Children (7-12 years)	5	11	57
Females (13+/Nursing)	4	10	61

EPA Baseline Assessment without Cranberries

Population	Percent RfD (RfD = 0.0017 mg/kg/day)		
	95th Percentile	99th Percentile	99.9th Percentile
US	4	7	23
All Infants	7	14	43
Nursing Infants	3	9	42
Non-Nursing Infants	8	15	43
Children (1-6 years)	7	13	44
Children (7-12 years)	5	9	32
Females (13+/Nursing)	3	7	25

The evaluation illustrates a clear reduction (reduced by one-half) in exposure to chlorpyrifos by eliminating cranberries as a route of exposure. This exemplifies the weakness of using field trial results in an acute dietary risk assessment and brings to question the validity of using only eight field residue data points to represent exposure of a single crop in the acute dietary risk assessment. For this reason, DAS supports the incorporation of residue monitoring data into the acute dietary risk assessment as a more realistic estimate of exposure to chlorpyrifos via cranberries. DAS also would like to note that this example points to the conservative nature of the acute dietary risk assessment wherein field trial data are used for seven other crops because a tolerance does not exist for these commodities.

DAS is especially concerned with the lack of statistical rigor in generating estimates of acute dietary risk. DAS does not believe that the 99.9th percentile estimates as they are currently derived are reliable or representative. DAS urges EPA to adopt a policy based on scientifically defensible exposure estimates. A more comprehensive discussion of this issue can be found in Wolt (1999) (a copy is enclosed with DAS' response submission).

In addition, DAS would like to point out the consistency between the risk assessments with and without cranberries at the 95th and 99th percentiles. This demonstrates that the lower percentiles are more resistant to unrealistic assumptions than the 99.9th percentile.

Page 8. "*For a number of commodities for which no chlorpyrifos tolerances have been established, PDP has found residues in more than one year of sampling. These include spinach, squash, and carrots. The residue data for these three commodities are summarized in Table 3 below. Residues were also detected in celery (4 samples in 1994, 0.005 - 0.045 ppm), potatoes (1 sample in 1994, 0.024 ppm), and lettuce (1 sample in 1994 at 0.01 ppm).*"

DAS does not support the application of chlorpyrifos to squash, spinach, carrots, celery, potatoes, or lettuce. While it is true these crops do not increase exposure to chlorpyrifos, residues detected on these crops by PDP are illegal. Enforcement issues addressing illegal uses of pesticides are separate from risk assessment.

Page 9. "*Potential exposure to chlorpyrifos residues from consumption of fish was not addressed. No tolerances for fish are currently established. In 1992 the Agency Office of Water (OW) published a report (EPA 1992) that summarized chlorpyrifos residues found in freshwater fish at that time. The primary focus of the study was monitoring for dioxin/furan in fish. However, chlorpyrifos residues were detected in 26% of the 388 sites tested, with median, mean, and maximum concentrations of non-detect, 4.09, and 344 ppb respectively. This study indicated that consumption of freshwater fish could contribute to dietary exposure to chlorpyrifos. FDA also has monitored fish for chlorpyrifos. Of all fish and crustacean samples tested between 1992 to 1998, FDA found residues of chlorpyrifos in one trout (1994) and twelve catfish (four catfish in each year 1992 - 1994). FDA has found no residues of chlorpyrifos in any fish from 1995 to 1998.*"

Any residues of chlorpyrifos found in fish would be accidental and inadvertent because a tolerance does not exist for fish. Again, this issue should be separate from the assessment of acute dietary exposure to chlorpyrifos.

"*No cooking factors could be incorporated in this dietary exposure analysis. If Dow has any such data they should be supplied to the Agency (this was noted in a memo from HED (S. Knizner) to Dow on 4/7/95).*"

DAS recognizes further reduction of residues of chlorpyrifos is evident upon processing and cooking. Processing and cooking studies are a valuable tool for obtaining a more realistic estimate of exposure to chlorpyrifos. Cooking studies for chlorpyrifos-methyl have shown a clear reduction in residues upon cooking. It is probable residues of chlorpyrifos would also significantly reduce during the cooking process. DAS welcomes the opportunity to work with the Agency to consider valid extrapolations from existing cooking data for chlorpyrifos-methyl and evaluate possible cooking studies that could help to make the assessments realistic. In addition, the Apple Processors Association (APA) has worked closely with the Agency and industry to develop a database examining the reduction of residues upon processing. When the data is available, it should be considered for the purposes of risk assessment.

Page 11. *For the commingled apple food forms using the PDP data an RDF was created with 897 zeros, 587 at LOD of 0.0025 ppm and 425 positive findings. For commingled food forms from the market basket study, the RDF was 94 zeros, 37 at ½LOD of 0.001 ppm and 69 positive findings.*"

Incorrect formation of residue distribution file -- the sum of the data in the residue data file (RDF) created using PDP data does not equal the total number of samples collected by PDP (897 + 587+ 425 = 1909).

Page 20. *The specific RDF created for cabbage was 378 zeros, 105 samples at 1/2LOD of 0.00015 ppm and 11 positive results. The RDF for cauliflower was 164 samples at zero and 92 samples at the 1/2LOD of 0.00015 ppm. The RDF for bok choi was 95 samples at zero and 1 positive result at 0.2 ppm. The RDF for collards was 128 zeros, 15 at ½LOD of 0.00015 ppm and 4 positive results as noted in the table above. The RDF for kale was 108 zeros and 5*

positive results as noted above. The RDFs for mustard greens and kohlrabi had 143 zeros and 4 positive results from collards."

Incorrect formation of residue distribution file -- the sum of the data in the RDF created using PDP data does not equal the total number of samples collected by PDP (378 + 105 + 11 = 494).

Page 31-32. "*During the years 1992 to 1997 FDA analyzed 723 samples of strawberries with 8 positive findings up to 0.043 ppm. BEAD estimates that 12% of strawberries are treated with chlorpyrifos. Because strawberries are construed to be commingled these results were used directly without decomposition. The RDF consisted of 636 zeros, 87 set at the weighted ¼LOD of 0.00015 PPM, and the 8 positive findings.*"

Incorrect formation of residue distribution file -- the sum of the data in the RDF created using PDP data does not equal the total number of samples collected by PDP (636 + 87 + 8 = 731).

A revised estimate of acute dietary exposure to chlorpyrifos was determined employing refinement outlined in this response section. Popcorn, garlic, beets, and beet greens were removed because a tolerance does not exist for these commodities. A table is presented summarizing the results. We are providing results at 95th and 99th percentiles in our revised assessments to more accurately describe exposures, over the upper end of the distribution.

Revised Risk Assessment (EPA Proposed RfD)

Population	Percent RfD (RfD = 0.0017 mg/kg/day)		
	95th Percentile	99th Percentile	99.9th Percentile
US	4	7	20
All Infants	7	14	45
Nursing Infants	3	10	49
Non-Nursing Infants	8	15	40
Children (1-6 years)	7	13	44
Children (7-12 years)	5	9	30

Females (13+/Nursing)	3	7	25

Revised Risk Assessment (DAS Proposed RfD)

Population	Percent RfD (RfD = 0.05 mg/kg/day)		
	95th Percentile	99th Percentile	99.9th Percentile
US	0.13	0.25	0.77
All Infants	0.24	0.48	1.51
Nursing Infants	0.10	0.33	1.68
Non-Nursing Infants	0.27	0.52	1.45
Children (1-6 years)	0.25	0.45	1.51
Children (7-12 years)	0.16	0.32	1.07
Females (13+/Nursing)	0.11	0.23	0.86

2. Comments Pertaining to the Chronic Non-Cancer Dietary Exposure Assessment for Chlorpyrifos Dated June 1, 1999

Page 1. "*Exposure/risk exceed the Agency's level of concern for the general US population and various population subgroups when the assessment includes a default ½LOD value for all commodities without tolerance due to the micro-encapsulated food handling establishment use*."

Page 1. "*With respect to food handling establishment uses, we note that the assumption was made that ½LOD (0.005 pm) in all food without a tolerance due to presumed use of the microencapsulated formulation. This is a conservative assumption which should be considered when evaluating these estimates and interpreting these results.*"

The EPA has made advances in refining the estimates of exposure from direct-labeled applications of chlorpyrifos to crops. However, the background assumptions, default input values, and an entirely inappropriate method for including potential exposures from use of chlorpyrifos in FHE into the chronic dietary assessment are in error from both regulatory and scientific perspectives. These assessments produce grossly exaggerated and unrealistic estimates of risk. The errors are so significant, release of these inaccurate estimates without correction will be misleading to the agricultural community and the public. Without the inappropriate inclusion of the theoretical exposures from FHE uses, the EPA assessments realistically show chronic dietary risk is well

within acceptable levels. The results that suggest chronic dietary exposures to any population groups exceed acceptable levels are in error for the following reasons:

- Default assumptions for inclusion of potential residues from treatment of FHE in the current assessments increase theoretical exposures from only 25% of the RfD proposed by the Agency to 790% for the highest exposed population, implying exposure from indirect residues is 30 times greater than direct applications to crops. This result does not match with either scientific or common logic. Also, the available data contradict this prediction and do not indicate any increase in exposure from these treatments.
- No scientifically-accepted final EPA policy for incorporation of potential exposure from FHE treatments exists, but based on draft EPA policy, these uses should be considered "essentially

- The current assessment approach contains illogical assumptions that greatly overestimate even the chance of exposure. For example, the model simulation assumes that treatment to an FHE produces residues in all tap water consumed by an individual over their lifetime; even water not produced in or consumed at the FHE.

The approach used for inclusion of FHE has the effect of inserting a Tier I-type (discrete, tolerance-based values) default assumption into an otherwise higher-tier dietary assessment. This is a clear overestimation of chronic exposure to chlorpyrifos and is an error that nullifies an otherwise sound attempt to assess dietary exposure. The EPA has worked with scientists within government, industry, and academia to improve their dietary assessments, and DAS welcomes the opportunity to work further with EPA addressing the issue of FHE tolerances and producing realistic and scientifically-sound assessments of exposure and risk.

The approach used did not follow any finalized, scientifically-accepted EPA policy. In fact, draft policies would suggest a different approach. In the draft policy "Proposed Threshold of Regulation Policy Defining When a Food Use Does Not Require a Tolerance" (EPA Draft 11/30/98), uses which produce no detected residues are consider "essentially zero" exposure.

The draft policy states “Pesticides directly used near food, such as insecticides or rodenticides used in areas where food is stored, transported, prepared or served, may also be eligible for consideration under this proposal.” The available data contradict the results of the assessment showing a significant impact on exposures from FHE uses of chlorpyrifos, and, in fact, support classification of these uses as “essentially zero” exposure.

In the residue section for FHE uses on pages 13 and 20 of the “Revised Product and Residue Chemistry Chapter of the HED Chapter,” the Agency recognizes the unlikely occurrence of residues from these uses and states “no detectable residues are likely to occur in food items.” Inclusion of a quantifiable residue, at any level, contradicts this conclusion. In addition to the FHE residue study, the marketbasket study submitted to EPA by DAS showed no quantifiable residues in most food sampled from grocery shelves. These results indicate potential indirect residues from treatment in FHE are not increasing the magnitude of residues in the food items significantly and definitely do not increase exposures to the levels predicted by the EPA assessment.

The most significant contributor to the estimated high exposure levels in the EPA assessment of the impact of FHE uses is through consumption of water. Because direct application to water is not permitted in these uses, residues could only occur if the water came into contact with a treated surface or residues in the air. Migration of residues of chlorpyrifos into the water would require significant contact time because “chlorpyrifos is practically insoluble in water” (Revised Product and Residue Chemistry Chapters of the HED Chapter of the RED; May 25, 1999) as opposed to the short-term contact time expected in FHE.

The assessment model itself also propagates several invalid assumptions of exposure through water consumption. By assigning a default residue value for water in FHE, the model implies that residue to **all** water consumed by the individual during their lifetime or period of chronic exposure, regardless of the source of the water. Even water not from the treated FHE, such as

that obtained from the home tap, is erroneously assumed to contain residues from the treatment to the FHE.

Even if indirect residues were expected from these uses, the probability of consuming food or water in a treated FHE would need to be considered to produce a realistic assessment. People seldom eat all their meals in FHEs, not all FHEs are treated (i.e., market share), and even when treated, FHEs applications are periodic. Assessment of exposures over chronic periods must recognize the resulting probability of exposure.

Page 3, Acute Dietary Assessment. "*The FQPA safety factor is applicable for all population subgroups due to the concern for the possible increased susceptibility of infants and children to adverse effects resulting from a single exposure to chlorpyrifos (as demonstrated in the Moser and Padilla study) coupled with the extensive use of this organophosphate insecticide and resulting potential for exposure.*"

Page 3, Chronic Dietary Assessment. "*The FQPA safety factor of 3x is applicable for all population subgroups due to the concern for the possible increased susceptibility of infants and children to adverse effects resulting from repeated exposure to chlorpyrifos (as demonstrated in the developmental neurotoxicity study) coupled with the extensive use of this organophosphate insecticide and resulting potential for exposure.*"

DAS disagrees with the proposition that there is an increased susceptibility of infants and children to adverse effects resulting from acute and repeated exposures to chlorpyrifos under labeled use conditions. The FQPA safety factor can be reduced to 1x since chlorpyrifos has been shown to possess no pre- and post-natal toxicity of concern at relevant human exposure conditions (see section on FQPA safety factor).

However, if used, the FQPA safety factor should only be applied for population subgroups that consider children. This is because all mammalian toxicology studies required to support EPA registrations, including developmental and reproductive studies conducted according to FIFRA guidelines and under GLP, have been submitted and judged by the Agency to be acceptable. EPA

has reviewed these reproductive and developmental toxicity studies and concluded that they have shown no pre- or post-natal effects of concern.

Page 4. "*Tolerances for chlorpyrifos are listed under 40 CFR 180.342, 40 CFR 185.1000 and 40 CFR 186.1000.*"

Based on the tolerances, DAS recommends removal of beets and beet greens from the assessment because no crop tolerances exist for these raw agricultural commodities.

Page 5. "*For purposes of this risk assessment, the exposure assessment termed "Tier 3/4" includes some market basket data (only for beef and pork), whereas the "Tier 4" assessment includes all available market basket data (total of 9 commodities in this case).*"

DAS supports the use of the Tier 4 assessment as the best understanding (to date) of exposure of the population to chlorpyrifos. Collection of samples in 1993 renders the data comparable to both FDA and PDP data because the FDA samples reported in 1992 are a summary of samples actually collected in 1991; likewise, samples collected by PDP in 1994 are a summary of samples collected in 1993. Furthermore, product use patterns have not changed significantly since 1993; therefore, the magnitude of residues detected in subsequent years is not expected to increase. Also, percent market share from BEAD estimates have decreased so the frequency of detection would not be expected to increase. The number of samples collected for the marketbasket survey is also sufficient as a minimum sample size was determined using statistically validated procedures as published by Bolles et al. (*J. Agric. Food Chem*, 1999). In Appendix C, a graph is shown comparing the similarity of the marketbasket data submitted by DAS and the PDP monitoring for 1996. The similarity between the data validates both the PDP monitoring data and the marketbasket data as measurements of residues encountered by consumers prior to food preparation. Additionally, "Supermarkets were the only type of grocery outlet sampled because many of the target food items were not available in convenience stores" (*J. Agric. Food Chem*, 1999). The marketbasket data are a more realistic estimate of residues because the methods utilized to analyze samples are more sensitive.

"*Therefore, an additional set of dietary exposure assessments have been performed including results for squash, spinach, and carrots – three commodities frequently fed to infants and children.*"

DAS does not support the application of chlorpyrifos to squash, spinach, or carrots. Residues detected by PDP are illegal. Enforcement issues addressing illegal uses of pesticides are separate from risk assessment.

Pages 9-14. EPA should incorporate data from the marketbasket survey submitted by DAS for apple juice and orange juice. The table summarizing exposure below represents corrected residue values. The residue file incorporating these changes is included as an attachment (see Appendix C).

Revised Chronic Dietary Risk Assessment

Population	Exposure	DAS RfD (0.01 mg/kg/day) %RfD	EPA RfD (0.0001 mg/kg/day) %RfD
US	0.000017	0.2	17
All Infants	0.000016	0.2	16
Nursing Infants	0.000010	0.1	10
Non-nursing Infants	0.000019	0.2	19
Children (1-6 years)	0.000041	0.4	41
Children (7-12 years)	0.000026	0.3	26
Females (13+/nursing)	0.000020	0.2	20

3. Comments Pertaining to the Anticipated Residues for Chronic Dietary Exposure Assessment Document Dated June 1, 1999

The Agency has not included values used for the LOD and the average residue values for each crop prior to incorporation of percent crop treated so DAS can verify the anticipated residues used in the dietary risk assessment. Because of the abundance of data available from the monitoring programs, a more thorough assessment by DAS of the mean values and the values used for the LOD on each crop is necessary.

Page 2. "*Briefly, these calculated mean pesticide residues are preferentially obtained from either USDA PDP, FDA monitoring programs or market basket.*"

If the sources of monitoring data are listed in order of preference, the data from marketbasket studies should take priority over federal monitoring programs because marketbasket data represents the most refined measurement of residues prior to consumer purchase.

Page 5. "*A total of 860 samples of apple juice were analyzed by PDP in 1996 and 1997.*"

A more appropriate and applicable source of juice data is the marketbasket survey submitted by DAS. Marketbasket data is available for apple juice and shows only two samples with quantifiable residues. The correct value for apple juice is 0.0004 ppm. Using the marketbasket data for juice is consistent with the acute dietary risk assessment completed by the Agency.

"*Beets: Root and tuber percent crop treated estimates were used from BEAD.*"

A tolerance does not exist for beets. Therefore, beets should be removed from the assessment.

"*Orange Juice/Grapefruit Juice/Lemons Juice/Citrus: EPA will use the USDA generated Pesticide Data Program (PDP) monitoring data in its chlorpyrifos risk assessment.*"

A more appropriate and applicable source of juice data is the marketbasket survey submitted by DAS. Marketbasket data is available for orange juice and shows only one sample with

quantifiable residues. The correct value for orange juice is 0.001 ppm. Using the marketbasket data for juice is consistent with the acute dietary risk assessment completed by the Agency.

Page 6. "*Cranberries: . . .field trial data will be used instead.*"

DAS is aware the Agency will receive monitoring data from The Cranberry Institute. This data will reflect realistic residue levels actually encountered rather than limited, worst-case field trial data.

"*Kiwi Fruit: BEAD did not report a percent crop treated for kiwi so 100% was used as a default value.*"

This is an extremely conservative assumption and should be noted as such. DAS requests the opportunity to investigate more accurate estimates.

Page 17. "*Food Handler Establishment Food handling establishment tolerance is not currently set, however, for purposes of a chronic dietary exposure anticipated residue value, 0.01 ppm with a percent crop treated of* "

Incomplete sentence. Percent crop treated should be incorporated.

"*Commodities which are not currently registered for use with Chlorpyrifos.*"

Residues occurring in commodities not currently registered for use with chlorpyrifos are accidental and illegal. Detection of illegal residues is a separate issue from dietary risk assessment.

4. Comments Pertaining to the Chlorpyrifos – Possible Reduction of Residue Studies Document Dated April 17, 1995

DAS recognizes further reduction of residues of chlorpyrifos is evident upon processing. Processing studies are a valuable tool for obtaining a more realistic estimate of exposure to

chlorpyrifos. Cooking studies for chlorpyrifos-methyl have shown a clear reduction in residues upon cooking. It is probable that residues of chlorpyrifos would also significantly be reduced during the cooking process. Minor comments are included in this response.

Page 1. "*You also noted that a market basket survey is already in preparation by the registrant.*"

A marketbasket survey has already been submitted to the Agency by the registrant.

Page 2. "*Residues in the raw agricultural commodities should be well above the analytical method of determination so that the decline in residues can be accurately measured.*"

As clarification, the purposes for conducting a reduction of residues study would be to determine processing factors or reduction factors of chlorpyrifos upon processing. It should be noted that this approach is not an accurate measurement of residues of chlorpyrifos in the finished product, but only an estimate of the empirical difference between initial residues in the raw agricultural commodity and the finished product.

"*As you have noted, acute dietary exposure to chlorpyrifos is of concern.*"

This statement was made prior to incorporation of residues from monitoring programs and marketbasket surveys into the acute dietary risk assessment. Acute dietary exposure to chlorpyrifos is less than 50% of the RfD proposed by the Agency for the highest exposed population and well within acceptable limits when default residues from cranberries are eliminated from the assessment.

"*Therefore, to be most useful, a market basket survey should analyze single servings of commodities.*"

Statistical methods are in place to estimate residues of a given pesticide on a single serving. The Agency should also consider composite samples from marketbasket surveys in dietary risk assessment as they have done for monitoring data.

5. Comments Pertaining to the Chlorpyrifos – Revised Product and Residue Chemistry Document Dated May 25, 1999

Page 2, paragraph 2. The melting point range for technical chlorpyrifos is 41.5-**42.5**°C.

Page 4, Table 1. Add Dow AgroSciences LLC under the Registrant column for the 62719- MPs.

Page 7, Table 3.

62719-7	Dursban 2EC Insecticide	**Canceled** effective 11/27/96
62719-166	XRM-5184 L.O. Insecticide	Correct name is **Dursban Pro**
62719-200	B&G Dursban 2E Insecticide	**Canceled** effective 9/3/97
62719-46	Dow Dursban WB05	Correct name is **Dursban WB05**
62719-206	Dursban WB05 II	**Canceled** effective 9/21/98
62719-220	Lorsban 4E-HF	Correct name is **Lorsban-4E**

Page 7, Table 3 footnotes. Additional SLNs:

SLN #	**EPA Reg. # (62719-)**	**Crop**
AZ-870006	39	Brassica
CA-860066	39	Brassica
ID-950013	220	Sugar beets
MO-890008	34	Alfalfa
NM-950001	221	Peppers
TX-950011	221	Peppers

Page 16, PP#3F02872/3H05393. Grape pomace is no longer listed as a processed commodity (Ref: Table 1 of OPPTS 860.1000); therefore, the need for a 4 ppm feed additive tolerance is negated.

Page 29, mint. The raw agricultural commodity actually analyzed for chlorpyrifos was the leaves and stems (MRID 00034031), not the field-dried hay. Therefore, additional data should not be required for peppermint and spearmint tops (leaves and stems).

Page 35, Appendix I. Dursban* 6R insecticidal concentrate, 62719-51, canceled effective 1/28/98.

Page 36, Appendix I. Dursban 6 insecticidal concentrate, 62719-10, canceled effective 1/28/98.

Page 37, Appendix I. Dursban MCR Insecticidal Concentrate, 62719-49, canceled effective 1/28/98.

Page 41, Appendix I. DAS has submitted product chemistry packages for two of the three products listed in anticipation of reregistration requirements.

62719-76	44871701, 44871702, 44871703
62719-225	42119001, 42119002, 42119003

C. Water Exposure

1. Comments Pertaining to the HED Preliminary Risk Assessment Document Dated July 23, 1999

In the memorandum dated July 23, 1999 entitled "Chlorpyrifos: HED Preliminary Risk Assessment for the Reregistration Eligibility Decision (RED) Document," Table 6 presents the Acute and Chronic Risk from Drinking Water Exposure to Chlorpyrifos. DAS previously reviewed the Table 6 EFED recommended concentrations, which were originally proposed in a document dated November 13, 1998 and titled "Drinking Water Assessment of Chlorpyrifos." The November 13, 1998 document was attached to the June 1998 EFED Preliminary Ecological

*Trademark of Dow AgroSciences LLC

Risk Assessment. A detailed report of the DAS review was submitted to EFED in January, 1999 (Poletika et al., 1999). In this response document, the errors in the EFED drinking water assessment are enumerated, and initial corrected values for estimated chlorpyrifos concentrations in drinking water sources are provided. Following receipt of the HED Preliminary Risk Assessment in August 1999, additional review was performed and corrections were made to the erroneous EFED estimated concentrations. All of the Table 6 entries for concentration in the drinking water source recommended by EFED do not reflect our response and corrections to the earlier EFED assessments or the additional review of the HED document and, therefore, are in error.

Given below is the Original Table 6, followed by a version (Corrected Table 6) that presents corrected values for chlorpyrifos concentrations in drinking water sources and adjusted percent acute and chronic population adjusted dose (PAD) estimates. Note that the percent PAD estimates reflect both corrections in the recommended concentrations and use of the more appropriate PADs of 0. 05 mg/kg/day for acute exposure and 0.001 mg/kg/day for chronic exposure.

Original Table 6

Acute and Chronic Risk from Drinking Water Exposure to Chlorpyrifos

Drinking Water Source	Concentration (ug/L) (a)	Percent Acute PAD (b)			Percent Chronic PAD(c)		
		Adult Male	Adult Female	Child	Adult Male	Adult Female	Child
Groundwater, except where termiticidal application occurs	0.1	0.17	0.2	0.6	2.9	3.3	10
Groundwater, termiticide use areas	2000	3400	3900	12000	57000	67000	200000
Surface water, streams, rivers, reservoirs and lakes	0.4	0.67	0.78	2.4	11	13	40

(a) Concentrations for both acute and chronic exposures recommended by EFED.

(b) Acute PAD is 0.0017 mg/kg/day, which is comprised of the acute RfD of 0.005 mg/kg/day, with inclusion of the 3x FQPA safety factor.
(c) Chronic PAD is 0.0001 mg/kg/day, which is comprised of the chronic RfD of 0.0003 mg/kg/day, with inclusion of the 3x FQPA safety factor.

Corrected Table 6

Acute and Chronic Risk from Drinking Water Exposure to Chlorpyrifos

Drinking Water Source	Concentration (ug/L) (a)	Percent Acute PAD (b)			Percent Chronic PAD(c)		
		Adult Male	Adult Female	Child	Adult Male	Adult Female	Child
Groundwater, except where termiticidal application occurs	0.01 (d)	0.0006	0.0007	0.002	0.003	0.003	0.01
Groundwater, termiticide use areas	30 (e) (acute)	1.72.0	6.0				
	0.1 (f) (chronic)	0.006	0.007	0.02	0.03	0.03	0.1
Surface water, streams, rivers, reservoirs and lakes	0.4 (acute)	0.02	0.03	0.08			
	0.06 (g) (chronic)				0.02	0.02	0.06

(a) Concentrations for both acute and chronic exposures ARE NOT THOSE recommended by EFED, except for surface water, streams, rivers, reservoirs and lakes (acute only).
(b) Acute PAD is 0.05 mg/kg/day, which is comprised of the acute RfD of 0.05 mg/kg/day, with inclusion of the 1x FQPA safety factor.
(c) Chronic PAD is 0.0001 mg/kg/day, which is comprised of the chronic RfD of 0.01 mg/kg/day, with inclusion of the 1x FQPA safety factor.
(d) Concentration based on SCI-GROW run for field corn.
(e) Concentration based on Dow AgroSciences well remediation consumption re-start level.
(f) Concentration based on Dow AgroSciences well remediation monitoring cutoff.
(g) Chronic concentration based on:

One-third the 68-day time-weighted exposure cited in Poletika et al. (1999) to derive a conservative annual average for NAWQA data, (0.18 µg/L)/3 = 0.06 µg/L.

The mean daily concentration observed in one year of sampling of Orestimba Creek, CA (Poletika and Robb, 1998), 0.06 µg/L. The Orestimba Creek data is from an agriculturally dominated first-order stream receiving chlorpyrifos inputs during multiple application seasons.

The concentration recommended by EFED for groundwater, except where termiticidal application occurs, comes from a SCI-GROW run for 11 applications in sweet corn. The value is not particularly relevant for this assessment because 1) the sweet corn use represents a minute fraction of total chlorpyrifos use; 2) 11 applications are not economically viable for sweet corn growers, and, 3) the foliar treatments applied in sweet corn during plant maturation are not simulated

accurately by SCI-GROW (biased high). A more representative concentration estimate is presented in Corrected Table 6, based on the most important chlorpyrifos agricultural use in field corn.

SCI-GROW Run for Field Corn

```
RUN No.   1 FOR Chlorpyrifos        INPUT VALUES
 ---------------------------------------------------------------------
  APPL (#/AC)  APPL.  URATE    SOIL    SOIL  AEROBIC
  RATE          NO. (#/AC/YR)  KOC   METABOLISM (DAYS)
 ---------------------------------------------------------------------
    1.200      1       1.200     6070.0       30.0

 GROUND-WATER SCREENING CONCENTRATIONS IN PPB
 ---------------------------------------------------------
                    .010538
 ---------------------------------------------------------
A=    25.000  B=  6075.000  C=     1.398  D=     3.784  RILP=      .303
F=    -2.056  G=      .009  URATE=     1.200  GWSC=         .010538
```

DAS reminds HED that SCI-GROW is a very conservative model generally acknowledged within the Agency and by outside experts to be suitable only for screening purposes. Any exceedence of a drinking water level of comparison (DWLOC) based on a SCI-GROW prediction should be considered tentative and inappropriate for use in regulatory decision-making.

The EFED recommended concentration for chlorpyrifos in groundwater drinking water sources in termiticide use areas is 2000 μg/L. This recommendation comes from the largest reported value from well contamination incident reports. Accidental movement into a well at the time of treatment is not the same situation as potential contamination of groundwater in an aquifer through leaching following a normal labelled application. In section F.1.4. below, a detailed discussion of this distinction is provided, and the significance for risk assessment and risk management is considered.

More appropriate values for chlorpyrifos groundwater concentrations in termiticide use areas, 30 μg/L for acute exposure and 0.1 μg/L for chronic exposure, are given in Corrected Table 6. These levels represent the concentrations in the DAS well remediation and monitoring program at

which residents are advised to re-start use of the affected private well for domestic consumption (30 μg/L, the acute health advisory level (HAL) for chlorpyrifos) and when monitoring ceases (0.1 μg/L, the existing analytical method level of quantitation (LOQ)). The following line of reasoning justifies selecting 30 and 0.1 μg/L to be the correct concentrations for exposure assessment; at the level cited by EFED for the typical well contamination event, 2000 μg/L, it is almost certain that the well would be included in the well remediation program.

DAS agrees that the EFED recommendation for a maximum acute exposure in surface water sources of drinking water, 0.4 μg/L, can be taken from the maximum observed concentration in the National Water Quality Assessment Program (NAWQA) Group 1 data set. This is not necessarily the value expected in finished drinking water following treatment, blending, and distribution to users, which is probably lower. DAS strongly disagrees that this same concentration, 0.4 μg/L, can represent a chronic exposure; long-term exposure is more appropriately based on a time-weighted annual average. In Corrected Table 6, we provide a corrected value for a maximum expected chronic exposure in source water (again, not the expected concentration in finished water).

Footnote (g) in Corrected Table 6 explains the methods and data used to calculate the corrected estimate, 0.06 μg/L. Note that the two methods, using independent data sets, give identical results. The first method takes the 68-day time-weighted concentration in the NAWQA White River Basin identified by EFED as a representative seasonal level for chlorpyrifos and applies a conservative factor of three to convert the 68-day estimate to the necessary annual average. Because one can argue that the flowing water system in the White River Basin of Indiana may not represent the most vulnerable water body, the second method uses data from a source that is in the category of most vulnerable. Orestimba Creek, California is a primary agricultural drain that receives spray drift, irrigation tailwater, and winter runoff inputs of OP insecticides each year. This is a first-order stream with relatively low flow volume. During the year-long period of daily monitoring in the study cited in Corrected Table 6, footnote (g), numerous chlorpyrifos applications were documented in the watershed, along with many concentration peaks in the

creek. The directly calculated annual average concentration for this system, 0.06 μg/L, can be considered an upper bound for chronic exposure in source water (not finished water) taken from a vulnerable surface water body.

D. Agricultural, Occupational and Residential Exposure and Risk Assessment

1. Comments Pertaining to the Agricultural and Occupational Exposure Assessment Dated July 22, 1999

DAS' review of the "Agricultural and Occupational Exposure Assessment and Recommendations for the Reregistration Eligibility Decision Document for Chlorpyrifos" for uses on sod farms and on ornamentals highlights a number of EPA errors, significant issues in how the risk assessments were conducted, and assumptions used regarding product use and the marketplace.

- For some of the risk assessments run by EPA, the products chosen for exposure simulation were often not representative of labels or formulations currently in the marketplace. For example, EPA ran risk assessments on dry flowable formulations which are no longer sold by DAS. In addition, for wettable powders, label use information was taken from Dursban 50W Nursery in Water Soluble Packets specialty insecticide, also no longer sold, instead of from the Dursban 50W Insecticide label. Since DAS has continually worked to improve our products, conducting risk assessments for products no longer in the marketplace or formulations that have been discontinued may seriously overestimate overall exposure to chlorpyrifos since these products or labels are not being used and do not reflect current exposure scenarios. DAS suggests that EPA work with both DAS and the registrants of the non-DAS products to limit its risk assessments to commercially available products so that real world exposures can be accurately defined.
- In the risk assessments on non-agricultural uses conducted by EPA, product use inputs were often taken from insecticide generic use databases or extrapolated from agricultural use scenarios. In many cases, these are not accurate or applicable scenarios for the typical non-agricultural use of chlorpyrifos, and the risk assessments derived from these assumptions overestimate the actual exposure and risk for these products. To help provide a better

understanding of actual chlorpyrifos urban pest market usage and allow more refined assessments, DAS commissioned a small qualitative market research study by Mar-Quest in 1999. The information from this survey can be used to further advance risk assessments for these uses. DAS has provided the results of the survey with this response. DAS recognizes the challenges of interpreting the many varied uses in this market and offers our assistance to the Agency in analyzing and understanding our labels, typical use patterns, and the survey data in more detail.

- In many instances EPA conducted exposure and risk assessments on maximum and "predominant maximum" exposure scenarios. For urban uses, we are unable at this time to comment on errors for some of these assessments since the input parameter of the predominant maximum rate was not adequately defined. For example, EPA indicates the labels used to select the predominate maximum rates, but gives no information as to the use sections from the labels from which the maximum rates were chosen or the methods by which it determined what is predominant. In addition, the maximum rate for urban uses were combined with the maximum rates for agricultural uses, which provided average maximum rates that are incorrect for the specific market segments the exposure assessment tries to simulate. In addition, EPA ran risk assessments which did not include the label mandated personal protective equipment (PPE) or closed system packaging such as water soluble bags. In some scenarios the compounding conservatism and even errors of using predominant maximum rates, improper PPE, and no consideration of closed system packaging where appropriate, significantly overestimate the actual exposure. DAS requests the Agency consider these exposure reduction practices in its assessments to provide more realistic estimates of exposure and risk for both typical and maximum use scenarios.
- A number of the risk assessments are for product use scenarios that are inaccurate reflections of actual use in the marketplace, thus generating exposure scenarios that do not truly reflect real world exposure and risk. An example used throughout the document includes a risk assessment for use of chlorpyrifos on sod farms at the maximum rate for grub control via aerial application. In fact, such an application is impossible for a spray aircraft to accomplish due to the weight of the spray water it would have to carry (i.e., thousands of pounds of water

for the multiple acres needing to be treated). Another example is a risk assessment assuming chemigation as the method of application, when in fact DAS' urban labels all state "do not apply through any type of irrigation system." Also, an assessment was conducted for use of an airblast sprayer for treatment of tree bark for control of bark beetles and borers. Such applications are never made with airblast sprayers since complete coverage and penetration of the bark would not occur, which is required for effective plant protection. In addition, the maximum rates for stump treatments, bark treatments, and treatment of pine seedlings are switched. These current risk assessments greatly overestimate the amount of material handled and, thus, overestimate exposure. DAS requests EPA conduct revised risk assessments to better refine actual exposure risk for these examples, where applicable, and limit the risk assessments to commercially viable use patterns so that the assessments can be refined and actual exposures and risk can be realistically identified.

a. Products and Uses

The following comments are in response to the EPA's "Agricultural and Occupational Exposure Assessment and Recommendations for the Reregistration Eligibility Decision Document for Chlorpyrifos" dated July 22, 1999. Comments contained in this section include points relative to the agricultural and the non-agricultural uses of chlorpyrifos. Non-agricultural use comments pertain to the uses mentioned in the document specific to the turf and ornamental market segments as referenced from the labels of Pageant* DF specialty insecticide (EPA Reg. No. 62719-163), Dursban 50W Nursery in Water Soluble Packets specialty insecticide (EPA Reg. No. 62719-255), Dursban 50W in Water Soluble Packets specialty insecticide (EPA Reg. No. 62719-72), and Dursban Pro specialty insecticide (EPA Reg. No. 62719-166). In addition, three products included in the section review by EPA are not DAS registrations. These products are: Clean Crop Chlorpyrifos 4E Insecticide, EPA Reg. No. 34704-66, now owned by UHS; DuraGuard ME, EPA Reg. No. 499-367, owned by Whitmire; and, MEC Chlorpyrifos Livestock Premise Spray Concentrate, EPA Reg. No. 10350-22, owned by 3M. Since the existing Clean Crop Chlorpyrifos 4E Insecticide label has cited many of the use patterns from DAS Dursban 4E-N specialty insecticide label, EPA Reg. No. 62719-254, we have chosen to provide commentary also regarding UHS's label. In addition, DAS also commercially supports the

greenhouse uses of the Whitmire DuraGuard product, so comments will also be provided for their label. DAS will also comment on the livestock premise spray of the 3M label MEC Chlorpyrifos Livestock Premise Spray Concentrate. DAS recommends to the EPA that any matters associated with these non-DAS labels be discussed directly with the primary registrants of these products in addition to DAS.

DAS turf and ornamental comments pertain to this chapter's turf and ornamental chapter, which include only uses on sod farms, and treatment of ornamentals by the nursery, greenhouse, landscape, and arborist market segments. Treatments to lawns, golf courses, and by pest control operators and homeowners are not addressed in this chapter response, but are found in our comments to EPA's chapter titled "Occupational/Residential Handler and Postapplication Residential Risk Assessment for Chlorpyrifos" dated June 30, 1999 (see Appendix E).

Very little chlorpyrifos specific use pattern information at the level of the end user has been available in the past. Given the lack of such specific information, inputs for risk assessments were often taken from insecticide generic use databases or extrapolated from crop or agricultural use scenarios. To help provide a better understanding of actual chlorpyrifos urban pest market usage, DAS commissioned a small qualitative market research study by Mar-Quest in 1999. The information from this survey can be used to further advance risk assessments for these uses. We have provided the results of the survey with this response (see Appendix E) and highlighted selected results where applicable. DAS recognizes the challenges of interpreting the many varied uses in this market, and offers our assistance to the Agency in analyzing and understanding our labels, typical use patterns, and the survey data in more detail.

Although this study has a small number of surveys per market segment (i.e,. 11-14), DAS is of the opinion that, with very few exceptions, the median and mean responses fairly represent what we believe to be typical use in the field given our professional experience selling chlorpyrifos for over thirty years. DAS recognizes there was one question in the survey which was poorly designed and, thus, the answers obtained from the question are not used in our comments back to EPA.

This question was "what is your percent split in the use of the average rate versus the maximum rate per acre (or per 100 gallons) of chlorpyrifos or Dursban." This question intended to accommodate the multiple use pattern sites/pests on our labels, each of which has a minimum and maximum use rate. The respondents misinterpreted this question by superimposing their response for the label's maximum use rate for one use site/pest on to the maximum use rates for other sections of the label's use sites/pests and, since these maximum use rates differed from each other, the responses inaccurately reflect information specific to each use site/pest. Although included in the final survey results, DAS believes the results for this particular question are not accurate and should not be used. In addition, frequency of use information is collected as verbal commentary and was not quantifiable, although general trends can be inferred from the comments. This Mar-Quest study will be cited throughout our commentary and a complimentary copy of the study will be provided to EPA along with this response. To DAS' knowledge, this is the only chlorpyrifos specific use data collected in a manner to meet the needs of risk assessments that exists for urban market segments and so allows the refinement of the risk assessment beyond that possible using generic information.

Page 1. "*EPA Reg Nos: 62719-163, -39, -221, -23, -245, -255, -34; -79, -72, -166, -220, 34704-66, 499-367, and 10350-22.*"

Of the labels referenced in this chapter by EPA, Pageant DF (62719-163) is no longer being commercialized. DAS proposes that risk assessments based on this product are therefore not reflective of current uses. Also, Dursban 50W Nursery in Water Soluble Packets specialty insecticide (62719-255) is no longer being sold in the marketplace, but the uses on this label have been transferred, in part, to the Dursban 50W in Water Soluble Packets specialty insecticide label (62719-72), which is being sold in the marketplace. To reflect actual, current usage, risk assessments should be conducted for the water soluble packet (WSP) product, which offers significant reduction in exposure potentials. Dursban Pro specialty insecticide (62719-166), DuraGuard ME (499-367), and Clean Crop Chlorpyrifos 4E Insecticide (34704-66) are currently being sold. UHS has changed to an alternate brand name for their Clean Crop Chlorpyrifos 4E Insecticide product, now called Dursban TNP.

Page 3. "*Chlorpyrifos is formulated as many end use products including products intended for agricultural uses such as a wettable powder, granular, liquid flowable, dry flowables, soluble concentrate/liquids.*"

DAS is unaware of any liquid flowable formulations of chlorpyrifos currently being sold in the marketplace. As mentioned in the comments for page 1 above, there are currently no dry flowable formulations of chlorpyrifos sold by DAS.

"*Outdoor ornamental rates for wettable powders are up to 4 lb ai/acre and up to 0.16 lb ai/gallon for liquid formulations; and up to 8 lb ai/acre for fire ant control in sodfarm turf just prior to harvest. These rates are intended to reflect the upper range of application rates on the labels, and in some instances, the rates include the typical and/or predominant maximum rates. However, some of the rates assessed do not necessarily reflect the typical rates used on those crops such as the tobacco rate (i.e., 5 lb ai/A) and the fire ant sodfarm rate (i.e., 8.0 lb ai/A).*"

The maximum per acre ornamental use rate for the wettable powder (WP) formulation is 4 lb a.i./acre, but this high rate is used very infrequently and specifically for control of soil inhabiting insects via a preplant incorporation treatment and for control of scales on fruit, nut, and citrus tree stock grown by nurseries for retail sale. Preplant incorporation use makes up only 10% (mean response) of the overall number of chlorpyrifos applications per year by nursery growers (Mar-Quest, 1999). The 0.16 lb a.i./gal rate is indeed the maximum for liquids on ornamentals, but this is also a very infrequent use for treatment of pine seedlings to protect them from attack by pine weevils. There is a 6 gallons of dilute spray/acre restriction on the label (i.e., 0.96 lb a.i./acre). Pine seedling treatment use makes up only 1% (mean response) of the overall number of chlorpyrifos applications per year by landscapers, and none of the nursery growers surveyed made such treatments (Mar-Quest, 1999). The 8 lb a.i./acre rate is indeed the highest use rate for chlorpyrifos as a wettable powder for turf, but this is specific only to sod and the application is made just prior to harvest to meet USDA federal quarantine certification requirements for control of red imported fire ant (USDA, 1995).

The survey results indicate these scenarios do not represent the normal or typical use patterns. The typical use rate for wettable powders for nurseries is 0.5 lb a.i./100 gal (median response) and for liquids is 0.37 lb a.i./100 gal (median response) (Mar-Quest, 1999). For chlorpyrifos wettable powders on sod farms (excluding the fire ant 8 lb a.i./acre rate), the typical rate is from 1.3 to 3 lb a.i./acre (median responses) for surface and subsurface feeding insects, respectively (Mar-Quest, 1999). For chlorpyrifos liquids on sod farms (excluding the fire ant 8 lb a.i./acre rate), the typical rate is 2 lb a.i./acre (median responses) for surface and subsurface feeding insects, respectively (Mar-Quest, 1999).

As to the reference of "predominant maximum rates," DAS cannot comment on errors here since it is unclear what criteria EPA used to arrive at these values throughout the document. DAS requests further details on the process for determining the predominant use rates (i.e., use patterns cited, rates cited, statistical methods used to determine predominance) so we can comment. Based on our experience in these markets, DAS believes accurate and realistic estimates of risk and exposure cannot be developed by substituting use patterns and product labels of urban and agricultural markets. To properly assess exposure and risk for these uses, product and use specific assessments are necessary. DAS welcomes the opportunity to work with the Agency to better differentiate and understand these varied use patterns.

Page 4. "*It is reasonable to believe that uses of chlorpyrifos by commercial operators may encompass an intermediate-term duration. Private applicators, in most instances, are not expected to apply chlorpyrifos for more than seven consecutive days. No chronic (i.e., more than 180 days per year) agricultural or ornamental uses have been identified.*"

DAS agrees with this statement given the results in the Mar-Quest research study with one exception -- the sod farmer should be categorized as short-term duration. Sod farms apply chlorpyrifos on average three to five days per year (median response) for liquids and wettable powders for surface feeding insects, respectively; and, four to seven days per year (median response) for liquids and wettable powders for subsurface feeding insects, respectively (Mar-Quest, 1999). For fire ant quarantine applications, the frequency is six days per year (median

response) (Mar-Quest, 1999). It is highly unlikely such applications are made consecutively. Additional chlorpyrifos frequency of use information for other market segments are contained in the Mar-Quest research study provided to EPA with this response. DAS believes use of this chlorpyrifos-specific data can replace many of the assumptions used and allow further refinement of the risk assessments developed from general insecticide market research statistics.

"*The amount of chlorpyrifos assumed handled per day was derived from the various application rates and the number of acres (or gallons of spray solution) that could be applied in a single day.*"

DAS requests the Agency further refine and improve the risk assessments using the Mar-Quest chlorpyrifos-specific data rather than general insecticide market research statistics or generic assumptions.

"*. . .**baseline** attire (i.e., long pants, long sleeved shirts, no gloves) and only 3 of the 16 scenarios at the **maximum PPE** of coveralls over long pants, long sleeved shirts, and chemical resistant gloves while using open systems.*"

This baseline attire should incorporate the minimum labeled PPE requirements, which in addition to the above also stipulates the wearing of chemically resistant or waterproof gloves and/or footwear depending on the formulation. In addition, for the maximum PPE, labels such as Dursban 50W Insecticide also stipulate shoes plus socks, protective eyewear, and chemically resistant headgear for overhead exposures. The label for Clean Crop Chlorpyrifos 4E Insecticide also includes coveralls and a chemically resistant apron when cleaning equipment, mixing, and loading. DAS requests EPA to reassess exposure and risks using the PPE required on the specific product labels since this can differ for each product. Exposures cannot be accurately assessed and are overestimated by drawing across multiple labels at once. In addition, use of the appropriate, human-based NOEL increases to 16 the number of scenarios which contain acceptable MOEs.

"*There are insufficient information and data to assess the seed treatment uses, dip applications (e.g., preplant peaches), and dry bulk fertilizer applications to citrus orchard floors.*"

The particular products being referenced as dip applications are unclear in the document. Although the example is specific to use of Lorsban* under ag. practices, Dursban labels for nurseries and greenhouses also stipulate dip treatments of balled and burlapped or containerized plant stock to satisfy USDA Federal Fire Ant Quarantine Regulations (USDA, 1995), or requirements contained in the US/Canada Japanese Beetle Harmonization Plan (Elder et al., 1998) for transport of nursery stock. For dip treatments, Dursban or chlorpyrifos is the only product certified for such use with no alternatives allowed. For nurseries, 9% (mean response) do dip treatments using 58 gallons/day (median response) three days/year (median response). For greenhouses, 9% (mean response) do dip treatments using 200 gallons/day (median response) ten days/year (median response) (Mar-Quest, 1999). These treatments are made outdoors by greenhouses under nursery conditions. DAS requests EPA to reassess risks using the chlorpyrifos specific information contained in the Mar-Quest research study.

Page 5. "*Even though there are insufficient information (e.g., timing of applications -- dormant/bark versus foliar treatments) and exposure data to assess postapplication activities for ornamental, sodfarm, and soil incorporated uses, these uses are believed to require long REIs because of the high application rates and high potential for dermal contact.*"

Current turf and ornamental labels for worker protection standard (WPS) uses in nurseries, greenhouses, and sod farms already stipulate a restricted entry interval (REI) of 12 hours. DAS requests that any REI changes be based on MOEs calculated using NOELs based on human toxicity data. In addition, a longer REI for sod treated to meet the USDA Federal Fire Ant quarantine regulations may create additional regulatory problems since it would result in further dissipation of residues, thereby decreasing the required 42 days of certification protection of the sod once cut (USDA, 1995). For control of fire ants in cut sod, Dursban or chlorpyrifos is the only product certified for such use with no alternatives allowed. DAS requests EPA to reassess risks to also accommodate the additional post-handling PPE required for handlers of treated-cut-sod which stipulates the addition of elbow length waterproof gloves, chemical resistant apron, and chemical resistant footwear plus socks to the already mandated PPE under the WPS statement. In

*Trademark of Dow AgroSciences LLC

addition, the USDA regulations require a 48-hour period prior to handling treated sod (USDA, 1995).

"*The uncertainties include but are not limited to the following:*

- *exposure of an intermediate-term duration to assess all uses;*
- *extrapolating exposure and DFR data by the amount of active ingredient handled or applied;*
- *not all of the exposure data are of high confidence because of the lack of replicates and/or inadequate QA/QC in the studies;*
- *using crop-specific DFR data to assess other crops; and*
- *application timing in comparison to actual potential postapplication exposure scenarios*

"*These uncertainties are inherent in most pesticide exposure assessments. The conservative nature of the assessments, however, are believed to be protective of the handlers and reentry worker.*"

Given the data supplied in the Mar-Quest research study, DAS requests EPA reassess risks using the chlorpyrifos-specific use information provided. For bullet point one, the Mar-Quest data show sod farms should be considered short-term and not intermediate-term duration. DAS requests further information from EPA on what data would be helpful in answering the uncertainties.

Page 7.

Table 2. Chlorpyrifos Hazard Endpoints and Uncertainty Factors.

Route/ Duration	*NOAEL (mg/kg/day)*	*Effect*	*Study*	*Uncertainty Factors*[b]	*Comments*

For the column header "Uncertainty Factors," the footnote related to the superscript "b" appears to be missing from the table.

DAS believes the short term NOEL should be 0.5 mg/kg/day with an intraspecies factor of 10, and the intermediate- and long-term NOEL should be 0.1 mg/kg/day with an intraspecies factor of 10. Since both are oral NOELs, the inhalation exposure should be considered a part of the overall

expression of dose and added to the dermal dose (after correction of the dermal exposure for dermal absorption) prior to being compared to the NOEL to determine the MOE.

"*Typical vegetable crops range from 1 to 2 lb ai/acre (up to 2.75 lb ai/acre for radishes); granular applications up to 3.0 lb ai/acre for tobacco; greenhouse and outdoor ornamentals as high as 0.16 lb ai/gallon (ornamental bark treatments); sodfarm fire ant treatments up to 8 lb ai/acre; citrus 6 lb ai/acre; and tree nuts and fruits at 2 lb ai/acre.*"

The only chlorpyrifos product registered for use in greenhouses is DuraGuard ME by Whitmire, which has a maximum rate of 0.0066 lb a.i./gal and not 0.16 lb a.i./gal. The 0.16 lb a.i./gal rate is the maximum for chlorpyrifos liquids and wettable powders on ornamentals, but this is for a very infrequent use which is for treatment of pine seedlings in the landscape or by nurseries to protect them from attack by pine weevils (not bark treatment which has a maximum rate of 0.08 lb a.i./gal for bark beetles). In addition, there is a label restriction to not apply more than 6 gallons of dilution/acre (i.e., 0.96 lb a.i./acre). Pine seedling treatment use makes up only 1% (mean response) of the overall number of chlorpyrifos applications per year by landscapers and none of the nursery growers surveyed were making such treatments (Mar-Quest, 1999). The 8 lb a.i./acre rate is the highest use rate for chlorpyrifos as a wettable powder for turf, but this is specific only to sod and the application is made just prior to harvest to meet USDA federal quarantine certification requirements for control of red imported fire ant (USDA, 1995).

Page 8. "*Chlorpyrifos is formulated as a wettable powder (containing 50 percent a.i.), dust (containing 0.125 to 1.0 percent a.i.), granular (containing 0.14 to 15 percent a.i.), bait (containing 0.03 to 1.0 percent a.i.), liquid flowable (containing 0.5 to 30 percent a.i.), impregnated material (containing 0.9 to 10 percent a.i.), pellets/tablets (containing 0.5 to 1.0 percent a.i.), pressurized liquids (containing 0.25 to 3.8 percent a.i.), microencapsulate (containing 0.15 to 20 percent a.i.), dry flowables (containing 50 percent a.i.), soluble concentrate/liquids (containing 0.5 to 62.5 percent a.i.), and liquid ready-to-use (containing 0.22 to 1.0 percent a.i.).*"

DAS understands this chapter is confined to the turf and ornamental treatments that encompass the professional market segments of landscape, arborist, nursery, greenhouse and sod farms since use by lawn care, golf course, pest control operators and homeowners are addressed in another

HED chapter or appendix. Based on the scope of this chapter, the following formulations are either not labeled for the relevant markets of this chapter or are no longer sold and can be removed from this section:

Dust, bait, liquid flowable, impregnated material, pellets/tablets, pressurized liquids, dry flowables, and liquid ready-to-use.

"*Aerial (Spray) Equipment: foliar applications to fruit/nut trees, cranberries, field crops (e.g., alfalfa, sorghum/Milo, wheat, soybeans, corn), cotton, vegetable crops, specialty crops (e.g., Christmas trees, mint, peanuts, sunflowers), and sodfarms.*"

DAS is not aware of any use of aerial application for treatment of sod farms with chlorpyrifos. These treatments are made with a tractor-mounted boom sprayer. Aerial application is not a method of use that is applicable to sod farms for application of chlorpyrifos.

"*Chemigation Equipment: field crops, cotton, cranberries, specialty crops, and ornamentals. The exposure to the handlers using chemigation equipment is represented by the mixer/loader and the amount handled is assumed to be equivalent to that of the aerial applications.*"

DAS turf and ornamental labels specifically state do "not apply through any type of irrigation system." Chemigation is not a method of use that is applicable to ornamental treatments.

Airblast Equipment: fruit/nut/ornamental tree foliage and bark treatments."

Treatment of fruit and nut trees in a nursery operation is much different than in an orchard situation, where airblast sprayers are often used. In the nursery, fruit and nut trees are small transplants or whips that are generally treated using hydraulic sprayers with a handgun or with a backpack sprayer. Rarely is the stock allowed to mature to a size where it will set fruit. Ornamental bark treatments are also made to small transplants or whips and this is generally also treated using hydraulic sprayers with a handgun or with a backpack sprayer. In fact, the Clean Crop Chlorpyrifos 4E Insecticide label use directions for control of the elm bark beetle via bark

treatment specifies use of a backpack mistblower or hydraulic sprayer and not an airblast sprayer. In addition, use directions for control of peach tree borers via bark treatment specify to use a coarse low pressure spray. A coarse spray is also recommended for foliage treatments. Airblast is not a method of use that is applicable to treatment of tree foliage and bark in the nursery.

"*Dip: peach/nectarine transplants (no data are available to assess this use).*"

The products referenced by the dip application use are unclear. Although the example is specific to use of Lorsban under agricultural practices, Dursban labels for nurseries and greenhouses also stipulate dip treatments of balled and burlapped or containerized stock usually done to satisfy USDA Federal Fire Ant Quarantine Regulations (USDA, 1995), or requirements contained in the US/Canada Japanese Beetle Harmonization Plan for transport of nursery stock (Elder et al., 1998). For nurseries, 9% (mean response) do dip treatments using 58 gal/day (median response), three days/year (median response). For greenhouses, 9% (mean response) do dip treatments using 200 gal/day (median response), ten days/year (median response) (Mar-Quest, 1999). These treatments are made outdoors by greenhouses under nursery conditions. Depending on the scope of EPA's bullet point, dip treatments are applicable to nursery and outdoor greenhouse operations also.

"*There is also a turfgrass/sodfarm use specifically listed on the label to be applied with a "mistblower". This use is atypical for turf application and not addressed in this section because there are only three replicates in the Pesticide Handlers Exposure Database (PHED) with a mistblower for turf to base an exposure assessment (exposure for the three replicates are driven by the hand exposure). More information (e.g., how often is this equipment used, exposure data) should be submitted by the registrant on this type of application for turf.*"

This use is for a mist applicator to treat low underbrush, grassy areas, weeds, and ground surfaces and debris to control ticks and chiggers and rarely involves treatment of entire areas of turfgrass. This use is specific to lawn or park type turf where humans would encounter ticks and chiggers as a nuisance or disease vector. As such, the application is not appropriate for sod farms. DAS

agrees with the EPA that this use is atypical. A more typical application scenario is use of a backpack sprayer or hand-held hydraulic spray gun for non-sod farm or athletic field turf.

Page 9. "*(4) mixing/loading the dry flowable formulation to support aerial, airblast, and groundboom applications, (5) applying the liquid/dry flowable/ wettable powder/granular formulations with aerial equipment, (6) applying the liquid/dry flowable/wettable powder formulation with groundboom equipment, (7) applying the liquid/dry flowable/wettable powder formulation with airblast equipment.*"

As mentioned before, DAS no longer sells dry flowable formulations of chlorpyrifos into the marketplace and, thus, this formulation is not applicable for exposure scenarios.

Page 14. "*Chlorpyrifos labels include a multitude of uses and a wide range of application rates. Therefore, the rates presented in Table 3 are not all inclusive and an attempt has been made to assess the higher application rates to ensure that the exposures are not underestimated.*"

In addition to assessments conducted with maximum use rates, risk assessments should be run on typical rate and end use scenarios to more accurately reflect the majority of use in the marketplace. Limiting risk assessments to maximum rate scenarios overestimates the risk of actual typical use in the marketplace. DAS requests EPA to also run risk assessments on more typical use scenarios to assess such exposures that also make up the majority of chlorpyrifos use. The Mar-Quest research study should provide much of the needed typical use information specific to chlorpyrifos for the relevant market segments. This information should be incorporated into EPA's risk assessments.

Page 15. "*It is difficult to assess all of the "typical" agricultural uses (i.e., actual or predominate application rates and farm sizes), and therefore, an assessment has been developed which is believed to be realistic and yet provides a reasonable certainty that the exposures are not underestimated.*"

DAS recognizes the challenges of assessing such a complex use market, but to accurately assess real world risk, individual risk assessments for at least key and representative use patterns are necessary. For many uses, the current approaches overestimate exposure and risk. DAS is

willing to work with the Agency to better differentiate and define the individual use patterns in this market to allow further refinement of the risk assessments.

"*The 'predominant max' rate that is assessed is the most predominant maximum application rate for the specific equipment type and formulation.*"

As to the reference of "predominant maximum rates," DAS cannot comment on errors here since it is unknown what criteria EPA used to arrive at these values throughout the document. DAS requests EPA to provide details on the process for determining the predominant use rates in their risk assessment (i.e., use patterns cited, rates cited, statistical methods used to determine predominance) so we can comment appropriately.

"*The aerial sodfarm rate is assessed at 4 lb ai/acre (White Grub).*"

DAS is not aware of any use of aerial application for treatment of sod farms with chlorpyrifos. These treatments are made with a tractor-mounted boom sprayer. For control of grubs, applications are made in 4 gal/1000 sq ft of spray to be able to penetrate thatch followed by post-treatment irrigation. A pesticide spray aircraft cannot apply such a volume to multiple acres of turfgrass due to the weight of the water needed per acre (i.e., 1453 lb of water). Aerial application is, therefore, not applicable to sod farms.

Page 16. "*The daily acres treated or gallons applied are HED standard values (see Table 3) along with the amount of gallons that may be applied using handheld equipment.*"

To allow us to understand the assessments and comment appropriately, DAS requests EPA provide further details on the selection of their standard values and how these have been validated to represent real world typical or maximum use scenarios. DAS has provided with this response the results of the Mar-Quest research study which will assist in revising EPA's standard values used for risk assessments for chlorpyrifos. Although the Mar-Quest research is qualitative, it is the only information that DAS is aware of that currently exists to shed light on specific urban uses of chlorpyrifos.

"*However, the sodfarm fire ant rate is assessed at 10 acres because this is believed to be a reasonable maximum area that can be harvested in a single day and/or the area a commercial applicator might apply to multiple sodfarms in a single day.*"

To allow us to understand the assessment and comment appropriately, DAS requests EPA provide their rationale for what is listed as a reasonable maximum and how this has been validated to represent real world typical or maximum use scenarios.

"*Dry Flowable and Wettable Powder: Although there are no current labels for dry flowable and/or open bag packaging for wettable powders, these products are still registered and therefore included in this assessment.*"

All chlorpyrifos wettable powder formulations sold by DAS are currently in water soluble bags. DAS requests EPA to reassess human risks by incorporating the appropriate packaging used in the marketplace for their respective formulations. Water soluble bags are considered closed systems and, therefore, mitigate exposure risk significantly. Since dry flowable and open bag packaging are no longer sold and, therefore, not being used for dry flowables and wettable powders, assessments for these products are not reflective of current practices and overestimate real world exposure and risk.

"*While data from PHED provides the best available information on handler exposures, it should be noted that some aspects of the included studies (e.g., duration, acres treated, pounds of active ingredient handled) may not accurately represent labeled uses in all cases.*"

DAS agrees with this statement. Therefore, chlorpyrifos specific use information in the Mar-Quest market research study is provided to EPA with this response. DAS requests EPA reassess human risks using the chlorpyrifos specific data from this study and typical and maximum scenarios to further refine the assessments.

Page 17. "*These calculations of potential daily exposure to chlorpyrifos by handlers are used to calculate the absorbed doses and total risk to those handlers (see Occupational Risk section).*"

DAS requests EPA to also conduct risk assessments for typical use scenarios and not just maximum scenarios, which overestimate exposure for typical use which represents the predominant means by which chlorpyrifos is used in the marketplace.

Pages 18, 19, 20.

Table 3: Exposure Variables for Agricultural Uses (Including Non WPS Ornamental Uses) of Chlorpyrifos.

Exposure Scenario (Scenario #)	*Are Biological Monitoring Data Available?* [a]	*Application Rates (lb ai/acre)* [b]	*Daily Acres Treated* [c]
Mixer/Loader Exposure			
Mixing/Loading Liquids for Aerial/Chemigation Application (1a)	*Yes (447393-02)*	*1.5 predominant max / 4.0 sodfarm White Grub*	*350*
		3.5 citrus[d]	*100*
Mixing/Loading Liquids for Groundboom Application (1b)	*Yes (429745-01)*	*1.5 predominant max / 5.0 tobacco max*	*80*
		8.0 sodfarm fire ants (harvest only)	*10*
Mixing/Loading Liquids for Airblast Application (1c)	*Yes (431381-02)*	*2.0 predominant max such as Fruits & Nuts / 6.0 citrus*	*40*
		4.0 outdoor ornamental bark treatment	*10*
Mixing WP for Aerial/Chemigation Application (2a)	*No*	*2.0 predominant max / 4.0 sodfarm White Grub*	*350*
		3.5 citrus[d]	*100*
Mixing WP for Groundboom Application (2b)	*Yes (429745-01)*	*1.0 predominant max (brassica)*	*80*
		4.0 soil treatment ornamentals outdoors / 8.0 sodfarm fire ants (harvest only)	*10*
Mixing WP for Airblast Application (2c)	*No*	*2.0 predominant max / 6.0 citrus*	*40*
Loading Granulars for Aerial Application (3a)	*No*	*1.95 maximum aerial rate*	*350*
Loading Granulars for Ground Application (3b)	*Yes (3a & 8 combined*	*1.0 typical corn / 2.0 max corn / 3.0 maximum ground rate (tobacco)*	*80*

Exposure Scenario (Scenario #)	*Are Biological Monitoring Data Available?* [a]	*Application Rates (lb ai/acre)* [b]	*Daily Acres Treated* [c]
	444835-01)		
Mixing Dry Flowables for Aerial/Chemigation Application (4a)	*No*	*2.0 predominant max*	*350*
		3.5 citrus (no label, assumed same as WP label) [d]	*100*
Mixing Dry Flowables for Groundboom Application (4b)	*No*	*2.0 predominant max (assumed -- no label)*	*80*
		4.0 soil treatment ornamentals outdoors (assumed -- no label)	*10*
Mixing Dry Flowables for Airblast Application (4c)	*No*	*2.0 predominant max / 6.0 citrus (no label)*	*40*
Applicator Exposure			
Aerial (Spray) -- Enclosed Cockpit (5a)	*No*	*2.0 predominant max*	*350*
		3.5 citrus [d]	*100*
Aerial (Granulars) -- Enclosed Cockpit (5b)	*No*	*1.95*	*350*
Groundboom Tractor (6)	*Yes (429745-01)*	*1.5 predominant max / 5.0 tobacco max / 8.0 sodfarm fire ants*	*80*
Airblast Applicator (7)	*Yes (431381-02)*	*2.0 predominant max / 6.0 citrus*	*40*
		4.0 outdoor ornamental bark treatment	*10*
Tractor-Drawn Granular Spreader (8)	*Yes (3a & 8 combined 444835-01)*	*1.0 typical corn / 2.0 max corn / 3.0 maximum ground rate (tobacco)*	*80*
Seed Treatment (9)	*No*	*No Data*	*No Data*
Dip Application (Preplant Peaches) (10)	*No*	*No Data*	*No Data*
Flagger Exposure			
Spray Applications (11)	*No*	*2.0 predominant max*	*350*
		3.5 citrus [d]	*100*
Granular Applications (12)	*No*	*1.95*	*350*

Exposure Scenario (Scenario #)	*Are Biological Monitoring Data Available?* [a]	*Application Rates (lb ai/acre)* [b]	*Daily Acres Treated* [c]
Mixer/Loader/Applicator Exposure			
Backpack Sprayer (13)	*Yes (430279-01)*	*0.0417 lb ai/gal predominant max / 0.08 lb ai/gal bark beetle treatment / 0.16 lb ai/gal stump treatment*	*40 gal/day*
		3.5 citrus bark	*1 A/day*
		0.039 lb ai/gallon/750ft^2 animal premise fly treatment	*1,000 ft^2*
Low Pressure Handwand (14)	*Yes (430279-01)*	*0.0417 predominant max / 0.08 lb ai/gal bark beetle treatment / 0.16 lb ai/gal stump treatment*	*40 gal/day*
		3.5 citrus bark	*1 A/day*
		0.039 lb ai/gallon/750ft^2 animal premise fly treatment	*1,000 ft^2*
High Pressure Handwand (greenhouse uses) (15)	*Yes (430279-01)*	*Min. 0.0031 lb ai/gal*	*1000 gal/day*
		Max. 0.0063 lb ai/gal	
Hydraulic Hand-held Sprayer for Bark/Pine Seedling Treatment (16)	*No*	*3.5 citrus bark*	*10*
		0.08 lb ai/gal bark beetle treatment / 0.16 lb ai/ gal pine seedling treatment	*1,000*
		0.039 lb ai/gallon/750ft^2 animal premise fly treatment	*10,000 ft^2*
Dry Bulk Fertilizer Impregnation	*No*	*1.0 lb ai / 200 lb fertilizer / acre*	*No Data*

As to the reference of "predominant maximum rates" used throughout Table 3, DAS cannot comment on errors here since it is unknown what criteria EPA used to arrive at these values throughout the document. DAS requests EPA provide details on the approach used in determining the predominant use rates in their risk assessment (i.e., use patterns cited, rates cited, statistical methods used to determine predominance) so DAS can better evaluate the assessments

and comment appropriately. DAS supports running risk assessments on both typical and maximum use scenarios. DAS requests the EPA reassess their risk assessments using both of these scenarios.

The following comments apply to the exposure scenarios by number in EPA's Table 3 on pages 18-20. Unless referenced below by scenario number, the other excluded exposure scenarios are deemed to not be applicable to turf and ornamental uses given the crop information mentioned in EPA's Table 3. In addition, as mentioned above, until further information is provided on how the Agency determines the predominant maximum rate by product it is impossible for DAS to comment on errors or identify the market segments from which this information was taken. Throughout Table 3, DAS requests EPA provide the basis for their "daily acres treated" so that DAS can comment on errors.

Exposure scenarios 1a, 2a. DAS is not aware of any use of aerial application for treatment of sod farms with chlorpyrifos. These treatments are made with a tractor mounted boom sprayer. Aerial application is not a method of use that is applicable to sod farms for application of chlorpyrifos. In addition, labels specify to not apply through any type of irrigation system (i.e., chemigation).

Exposure scenario 1b. The only liquid chlorpyrifos product labeled and that is currently commercially used on sod farms at the 8 lb a.i./acre rate under the scope of the WPS (i.e., agricultural uses) is UHS's Clean Crop Chlorpyrifos 4E Insecticide. This scenario for a liquid formulation of chlorpyrifos should no longer exist for the UHS product since they have notified DAS they have petitioned EPA for removal of this use pattern from their Clean Crop Chlorpyrifos 4E Insecticide label.

Exposure scenario 1c. The only product labeled that is currently commercially used as a liquid for use under the scope of the WPS (i.e., agricultural uses) is the UHS product Clean Crop Chlorpyrifos 4E Insecticide. For bark treatment, the rate is 8 lb a.i./100 gallons of water to be applied as a dilute spray to tree trunks (i.e., bark) for beetle control and not 4 lb a.i./acre. This

treatment is made to individual trees as needed and not on an acre area basis. This type of treatment is done with a high volume spray to wet application using a spray gun usually with large droplet sizes. Application for beetle control as a bark treatment is never made with an airblast sprayer in nursery operations due to the poor coverage and inability to spray to wet. In addition, the spray is directed to the trunks only as specified on the label (treatment of the entire tree or its canopy as would occur with an airblast sprayer would be inappropriate and ineffective).

Exposure scenario 2b. The only chlorpyrifos wettable powder products labeled that are currently commercially used by nurseries and sod farms under the scope of the WPS (i.e., agricultural uses) are Dursban 50W Insecticide formulations. It should be noted that this is packaged in water soluble packets and, therefore, represents a closed system which provides significant reduction in exposure. DAS requests EPA incorporate the closed system scenario into their risk assessments. Although the maximum per acre ornamental use rate for the WP formulation is 4 lb a.i./acre, this high rate is used very infrequently and specifically for control of soil inhabiting insects via a preplant incorporation treatment and for control of scales on fruit, nut, and citrus tree stock grown by nurseries for retail sale. Preplant incorporation use makes up only 10% (mean response) of the overall number of chlorpyrifos applications per year by nursery growers (Mar-Quest, 1999). DAS also requests EPA provide background for selection of the 10 acres for the treatment unit for both sod and soil incorporation uses. DAS has supplied EPA with the Mar-Quest research study as part of this response and asks EPA to consider this information to reflect the use pattern of chlorpyrifos in their risk assessments.

Exposure scenario 4b. There currently no longer exists a dry flowable formulation being sold by DAS, so this use scenario is not a realistic representation of current use patterns for assessment purposes. DAS also questions the bridging of their assumption on the 10 acres for sod treatment over to the same acreage for treatment of soil for preplant incorporation applications, and requests further background for this assumption to allow appropriate comment.

Exposure scenario 7. The only products labeled that are currently commercially used under the scope of the WPS (i.e., agricultural uses) are the UHS product Clean Crop Chlorpyrifos 4E Insecticide and Dursban 50W Insecticide. For bark treatment, the rate is 0.08 lb a.i./gallon of water to be applied as a dilute spray to tree trunks (i.e., bark) for beetle control, and not 4 lb a.i./acre. This treatment is made to individual trees as needed and not on an acre area basis. This type of treatment is done with a high volume spray to wet application using a spray gun usually with large droplet sizes. Application for beetle control as a bark treatment is never made with an airblast sprayer in nursery operations due to the poor coverage and inability to spray to wet. In addition, the spray is directed to the trunks only as specified on the label (treatment of the entire tree or its canopy as would occur with an airblast sprayer would be inappropriate and ineffective). This scenario does not exist since airblast applications are not made for this use pattern in nurseries and rates per acre are not specified on the label.

Exposure scenarios 13, 14. The only products labeled that are currently commercially used for stump and bark treatment under the scope of the WPS (i.e., agricultural uses) are the UHS Clean Crop Chlorpyrifos 4E Insecticide product and our Dursban 50W Insecticide formulations. For stump treatment, the rate is 0.03 lb a.i./gal, not 0.16 lb a.i./gal. This application is for control of pales and northern pine weevil as a cut stump spray or drench. For bark treatment, the rate is 0.08 lb a.i./gal to be applied as a dilute spray to tree trunks (i.e., bark) for beetle control. The 0.16 lb a.i./gal rate is thus for treatment of pine seedlings as a full coverage spray and not as a stump treatment. Bark treatment is made to individual trees as needed with high volume spray to wet application using a spray gun usually with large droplet sizes. Although a backpack sprayer or low pressure handwand sprayer could be used in theory for small blocks of small plant material, this is not common practice for larger nursery operations. DAS requests EPA provide the background rationale for the selection of the 40 gal/day usage so appropriate comments can be provided.

Exposure scenario 15. The only product labeled that is currently commercially used in greenhouses under the scope of the WPS (i.e., agricultural uses) is DuraGuard ME sold by

Whitmire. This product is a microencapsulated liquid formulation. The minimum rate is 0.0033 lb a.i./gal and the maximum rate is 0.0066 lb a.i./gal (the product has 1.7 lb a.i./gal) and not 0.0031 or 0.0063 lb a.i./gal as based on EPA's calculations, which used the density of water. The use of a high pressure handwand is common practice in the greenhouse industry to be able to obtain full coverage of the plant. However, DAS requests EPA provide background rationale on the 1000 gal/day usage so appropriate comments can be made.

Exposure scenario 16. The only products labeled that are currently commercially used for bark treatment under the scope of the WPS (i.e., agricultural uses) are the UHS Clean Crop Chlorpyrifos 4E Insecticide product and Dursban 50W Insecticide formulations. For bark treatment, the rate is 0.08 lb a.i./gal of water to be applied as a dilute spray to tree trunks (i.e,. bark) for beetle control, and the 0.16 lb a.i./gal rate is for treatment of pine seedlings as a full coverage spray. Bark treatment is made to individual trees as needed and not on an acre area basis. Bark treatments are done with spray to wet application equipment using a spray gun with large droplet sizes. However, DAS requests EPA provide background rationale on the 1000 gal/day usage so appropriate comments can be provided.

The Mar-Quest research study is being provided to the EPA to aid in updating the use information in EPA's Table 3 and for incorporation into risk assessments for the typical use scenarios specific to chlorpyrifos for the turf and ornamental market segments for this chapter. DAS requests EPA incorporate this chlorpyrifos specific information into their risk assessment revisions. The Executive Summary is provided in Appendix E, and the full report will be submitted with this document.

Page 19. "*[b]Application rates are the maximum labeled rates found on EPA Reg. Nos. 62719-163, -39, -221, -23, -245, -255, -34; -79, -72, -166, -220, 34704-66 (Clean Crop Chlorpyrifos 4E -- sodfarm fire ant rate), 499-367 (499-367 is the only greenhouse label identified; the finished spray solution concentration assumed a density of water for the formulated product).*"

DAS has been notified by UHS that they have petitioned EPA for removal of the sod farm fire ant rate from their Clean Crop Chlorpyrifos 4E Insecticide label. The product 499-367 is DuraGuard ME from Whitmire and has 1.7 lb a.i./gal, which raises the minimum and maximum rate calculations for this product from EPA's density of water calculations of 0.0031 lb a.i./gal and 0.0063 lb a.i./gal to 0.0033 lb a.i./gal and 0.0066 lb a.i./gal.

Page 20. "***Predominant max"*** *in this table refers to the most* ***predominant maximum*** *application rate found on the labels for the specific formulation and equipment type. Typical rates are also included to characterize the chlorpyrifos uses. Not all application rates are included for all crops, instead, a cross-section of rates are used to represent the uses of chlorpyrifos.*"

As to the reference of "predominant maximum rates," DAS cannot comment on errors here since it is unknown what criteria EPA used to arrive at these values throughout the document. See previous comments on this subject.

"[c]*Daily acres treated are based on HED's estimates of acreage (or gallonage) that would be reasonably expected to be treated in a single day for each exposure scenario of concern. The sodfarm fire ant rate is restricted on the label for harvest only, therefore, this rate is limited to the amount of sod that may be harvested in a reasonable time frame. Therefore, using the limited data available, approximately 10 acres treated per day are assumed to be the upper range.*"

The chlorpyrifos-specific data per market segment provided from the Mar-Quest research study will allow further refinement of the risk assessments; we request EPA incorporate this into their risk assessments for typical use scenarios. In addition, DAS requests EPA provide the background rationale on their means to determine the estimates and what measures have been taken to validate that these actually reflect real world use scenarios.

Page 27.

High	*10,000*	*Harvest*	*1 (Reg. No. 62719-220)*	*Sunflowers (up to 1.5 lb ai/A), sugar beets, corn (up to 1.5 lb ai/A as a foliar treatment)*
			2 (Reg. No. 62719-220)	*Sweet potatoes, radishes (up to 2.75 lb ai/A), rutabagas (up to 2.25 lb ai/A)*
			8 (Reg. No. 34704-66-65783)	*Turfgrass (sodfarm) for fire ants*
		Cut/harvest, prune, transplant, ball/burlap	*1 (Reg. No. 62719-220)*	*Christmas trees*

DAS questions whether the high rating given to the treated sod handler for potential for dermal contact was made with the consideration of the additional PPE required in addition to the already required PPE from the WPS statement. The PPE requirement mandates a long-sleeved shirt and long pants, waterproof gloves, shoes plus socks, protective eyewear and chemical resistant headgear for overhead exposure. In addition, for handlers, there is a requirement of elbow-length waterproof gloves, chemical resistant apron, and chemical resistant footwear plus socks to reduce exposure. Also, the USDA fire ant regulations require a 48-hour period before handling treated sod (USDA, 1995).

Page 29. "*As described in the Handlers Exposure & Assumptions section, the short-term assessment is not provided in HED's traditional table format because uses of chlorpyrifos are assessed to be best represented by the intermediate-term duration.*"

The sod farmer should be categorized as short-term duration. Sod farms apply chlorpyrifos on average three to five days per year (median response) for liquids and wettable powders for surface feeding insects, respectively; and four to seven days per year (median response) for liquids and wettable powders for subsurface feeding insects, respectively (Mar-Quest, 1999). For fire ant quarantine applications, the frequency is six days per year (median response) (Mar-Quest, 1999).

It is highly unlikely such applications are made consecutively, so the current assessments overestimate exposure. DAS requests EPA assess sod farms under the short-term scenario.

Pages 30, 31.

> "*EPA calculated the baseline total MOE (short-term duration only) for each of the exposure scenarios using the following **baseline** PPE assumptions.*
>
> - *all occupational handlers are wearing footwear (socks plus shoes or boots);*
> - *occupational mixers and loaders using open mixing techniques are wearing long-sleeved shirts, long pants, and no gloves;*
> - *occupational applicators who use open cab airblast or tractor-driven application equipment and handlers flagging for aerial applications are wearing long-sleeved shirts, long pants, and no gloves; and*
> - *occupational handlers (mixers, loaders, and applicators) who use hand-held application equipment are wearing long-sleeve shirts, long pants, and no gloves.*
>
> "*If the baseline total MOE calculated using this baseline PPE was 100 or greater (since the NOAEL is based on data from animal studies) for an exposure scenario, then no further calculations were made. If the baseline total MOE was less than 100 for any exposure scenario, an additional total MOE was calculated based on increasing the level of PPE over the baseline PPE. HED calculated the additional-PPE total MOE for each occupational exposure scenario with a baseline total MOE of less than 100, using the following additional **PPE** assumptions:*
>
> - *all occupational handlers are wearing footwear (socks plus shoes or boots);*
> - *occupational mixers and loaders using open mixing techniques are wearing chemical-resistant gloves plus coveralls worn over long-sleeved shirts and long pants;*
> - *occupational applicators who use open cab airblast or tractor-driven application equipment and handlers flagging for aerial applications are wearing chemical-resistant gloves (except flaggers -- no gloves) plus coveralls worn over long-sleeved shirts and long pants; and*
> - *occupational handlers who use low pressure handwands are wearing chemical-resistant gloves plus coveralls worn over long-sleeve shirts and long pants.*
> - *Also, if necessary, a dust/mist mask represented by a 5-fold protection factor is added to mitigate the risks.*

"*If the additional-PPE total MOE calculated using this additional-PPE was 100 or greater (the NOAEL is based on data from animal studies) for an exposure scenario, then no further calculations were made. If the additional-PPE total MOE remained less than 100 for any occupational exposure scenario, an addition total MOE was calculated based on mandatory use of engineering controls where feasible. Engineering controls are not available for occupational handlers (mixers, loaders, and applicators) who use hand-held application equipment. HED calculated the engineering-control total MOE for each occupational exposure scenario with an additional-PPE total MOE of less than 100, using the following* ***engineering control*** *assumptions:*

- *all occupational handlers are wearing footwear (socks plus shoes or boots);*
- *occupational mixers and loaders handling liquid formulations using a closed system are wearing chemical-resistant gloves plus long-sleeved shirts and long pants;*
- *occupational mixers and loaders handling wettable powders using a closed system (water-soluble packages) are wearing long-sleeved shirts and long pants, and chemical-resistant gloves; and*
- *occupational applicators who use aerial, airblast, or tractor-driven application equipment and handlers flagging for aerial applications are located in enclosed cabs or cockpits and are wearing long-sleeved shirts and long pants, and no gloves.*"

Current label language differs from that cited by the Agency. In terms of occupational handlers for use patterns that involve turf and ornamental applications under the WPS, this would be confined to handlers of treated plant material, which is sod for sod farms, and nursery and greenhouse stock. Label requirements in the WPS section of products labeled and commercially sold into sod and nursery markets specify a 12-hour reentry interval. In addition, PPE requirements for these individuals coming into contact with treated plant material under commercial production practices specify coveralls (for wettable powders) or coveralls over short-sleeved shirt and short pants (for liquids); waterproof gloves (for wettable powders) or chemical resistant gloves (for liquids); shoes plus socks (for wettable powders) or chemical resistant footwear plus socks (for liquids); protective eyewear; and, chemical resistant headgear for overhead exposure. In addition, for treated sod, the PPE requirements also stipulate elbow-length waterproof gloves, chemical resistant apron, and chemical resistant footwear plus socks. The USDA fire ant quarantine regulations also require a 48-hour period prior to handling treated sod

(USDA, 1995). The Duraguard greenhouse product requires coveralls, waterproof gloves, and shoes plus socks.

For mixers/loaders and applicators for WPS uses, these labels specify PPE of long-sleeved shirt and long pants (for wettable powders) or coveralls over short-sleeved shirt and short pants (for liquids); waterproof gloves (for wettable powders) or chemical resistant gloves (for liquids); shoes plus socks (for wettable powders) or chemical resistant footwear plus socks (for liquids); protective eyewear; and, chemical resistant headgear for overhead exposure and chemical-resistant apron when cleaning equipment, mixing, or loading (for liquids). The Duraguard greenhouse product requires coveralls, waterproof gloves, and shoes plus socks.

Non-WPS ornamental use patterns (landscaper, arborist) for chlorpyrifos liquids requires long-sleeved shirt and long pants, chemical resistant gloves, chemical resistant foot wear plus socks, and protective eyewear (eyewear for UHS product Clean Crop Chlorpyrifos 4E Insecticide, but not for Dursban Pro specialty insecticide). For wettable powder formulations of chlorpyrifos, long-sleeved shirt and long pants, protective eyewear, water proof gloves, and shoes plus socks are required.

DAS requests EPA reassess risks using the label mandated PPE required for the exposure/application scenarios that represent existing commercial uses of these market segments. The current assessments do not represent current label language requirements and, therefore, are not accurate assessments of actual exposure and risk.

Page 39. "*Based on these concerns and lack of data, HED recommends that a REI be set using a comparable (or maximum) interval calculated from the existing data for other uses until more information is submitted by the registrant.*"

DAS feels any REI changes should be based on MOEs derived from the use of NOELs from human toxicity data.

Pages 41, 50, 64. "*Appendix A. Table A*"; "*Appendix B. Tables B1-B4*;" "*Appendix C. Tables C1-C8*."

DAS requests EPA consider the information/comments provided above, the new market-specific use pattern chlorpyrifos information provided from the Mar-Quest research study, and PPE as mandated on the labels to revise their risk assessments to reflect both typical and maximum use scenarios for products commercially sold in the market place with appropriate existing formulation/packaging and, given these reassessments, revise the content of Appendices A, B, and C. DAS believes consideration of this additional information allows significant refinement of the risk assessments to more accurately reflect exposures and risk in the real world.

Agricultural uses are addressed by the EPA chapter "Agricultural and Occupational Exposure Assessment and Recommendations for the Reregistration Eligibility Decision Document for Chlorpyrifos" dated July 22, 1999. EPA text is noted in italic font, DAS rebuttal/comments are noted in non-italic font.

Page 1. "*EPA Reg Nos: 62719-163, -39, -221, -23, -245, -255, -34; -79, -72, -166, -220, 34704-66, 499-367, and 10350-22.*"

Of the DAS labels referenced above, only 62719-220 (Lorsban-4E insecticide), 62719-245 (Lorsban 4E-SG insecticide), 62719-79 (Lock-On* insecticide), 62719-221 (Lorsban 50W in Water Soluble Packets insecticide), 62719-38 (Lorsban 50-SL specialty insecticide) and 62719-34 (Lorsban 15G granular insecticide), are commercially available agricultural use insecticides in the U. S. Registration number 62719-23 refers to an obsolete formulation of Lorsban 4E insecticide (62719-23) that was replaced by Lorsban-4E (62719-220) in January of 1995. Lorsban 50W Wettable Powder Insecticide (62719-39) was also discontinued as a commercial product in 1995 and all Lorsban 50W is now sold as Lorsban 50W in Water Soluble Packets insecticide (62719-221). The other labels referenced pertain to "agricultural" uses on sod farms and treatment of ornamentals by the nursery, greenhouse, landscape, and arborists. DAS recognizes that several of

*Trademark of Dow AgroSciences LLC

these obsolete products have maintained active registration numbers and will work with the Agency to delete unnecessary registrations. However, for the purposes of this preliminary risk assessment, only use patterns contained within the above six labels should be considered as representative of agricultural use of chlorpyrifos.

Page 3. "*Chlorpyrifos is formulated as many end use products including products intended for agricultural uses such as a wettable powder, granular, liquid flowable, dry flowables, soluble concentrate/liquids.*"

DAS is unaware of any liquid flowable formulations of chlorpyrifos currently being sold in the agricultural marketplace. As mentioned in the comments relative to page 1, there are currently no dry flowable formulations of chlorpyrifos being sold by DAS.

Page 4. "*. . .**baseline** attire (i.e., long pants, long sleeved shirts, no gloves) and only 3 of the 16 scenarios at the **maximum PPE** of coveralls over long pants, long sleeved shirts, and chemical resistant gloves while using open systems.*"

The baseline attire utilized in the risk assessment is not reflective of any PPE requirements for commercially available chlorpyrifos products currently used in agricultural production. All sprayable chlorpyrifos products have minimum PPE requirements that are more protective than the minimum baseline PPE utilized in the EPA preliminary risk assessment. Lorsban 15G insecticide has PPE requirements which are less than the EPA baseline PPE (no gloves required). Lorsban 15G is also only applicable to four of the exposure scenarios referenced in Table 3 (p 18), and is predominately used by private applicators where exposure would be short-term (one to seven days). In addition, use of the appropriate, human-based NOEL increases to 16 the number of scenarios which contain acceptable MOEs. The table below summarizes the PPE required on labels of agricultural use DAS chlorpyrifos products.

PPE Required	Lorsban-4E	Lorsban 4E-SG	Lock-On	Lorsban 50W in WSP	Lorsban 15G
Long-sleeved shirt and long pants			X	X	X
Coveralls over short-sleeved shirt and short pants	X	X			
Waterproof gloves				X	
Chemical-resistant gloves	X	X	X		
Shoes plus socks			X	X	X
Chemical-resistant shoes plus socks	X	X			
Protective eyewear	X	X	X		
Chemical-resistant headgear for overhead exposure	X	X		X	
Chemical-resistant apron when cleaning equipment and mixing or loading	X	X			

Page 14. "*Chlorpyrifos labels include a multitude of uses and a wide range of application rates. Therefore, the rates presented in Table 3 are not all inclusive and an attempt has been made to assess the higher application rates to ensure that the exposures are not underestimated.*"

DAS agrees with the EPA that risk assessments should be run on maximum rate exposure scenarios but believes that risk assessments should be also run on typical rate and use scenarios that more accurately reflect the majority of use in the marketplace. Limiting risk assessments to maximum rate scenarios overestimates the risk of actual typical use in the marketplace. DAS requests EPA also run risk assessments on more typical use scenarios to assess such exposures, which make up the majority of chlorpyrifos use. DAS has reviewed and agreed with quantitative usage information for chlorpyrifos developed by BEAD (BEAD, 1999). This information is useful to gain appropriate perspective of the agricultural use of chlorpyrifos in the United States and is useful data for the EPA to utilize to develop more realistic and accurate exposure scenarios as opposed to simplistic, overly conservative maximum use rate default assumptions.

Page 15. "*It is difficult to assess all of the "typical" agricultural uses (i.e., actual or predominate application rates and farm sizes), and therefore, an assessment has been developed which is believed to be realistic and yet provides a reasonable certainty that the exposures are not underestimated.*"

DAS recognizes the challenges in conducting assessments for such a broad and diverse market. However, the current approach of combining across use patterns and product labels results in serious errors and significant overestimation of exposures for many uses. To fairly and accurately assess exposure and risk for each use, individual assessments are needed. DAS welcomes the opportunity to work with the Agency to better understand our labels and the use patterns in these markets.

"*Dry Flowable and Wettable Powder: Although there are no current labels for dry flowable and/or open bag packaging for wettable powders, these products are still registered and therefore included in this assessment.*"

The products cited as no longer having current labels are also not being sold commercially into the use market so are not appropriate for inclusion in the asssessments. All chlorpyrifos wettable powder formulations sold by DAS are only available currently in water soluble bags with the exception of Lorsban 50-SL specialty insecticide, which is only labeled for use as a seed treatment (scenario 9, Table 3, p 19). DAS requests EPA reassess human risks by incorporating the appropriate packaging used in the marketplace for respective formulations. Water soluble bags are considered closed systems and, therefore, mitigate exposure risk significantly.

Pages 18, 19, 20.

Table 3: Exposure Variables for Agricultural Uses (Including Non WPS Ornamental Uses) of Chlorpyrifos. Refer to pages 78-80of this document to view Table 3. The following comments apply to the exposure scenarios by number in EPA's Table 3 relative to agricultural uses on pages 18-20. The comments below do not pertain to turf and ornamental uses. Comments are restricted to the products on Table E.4. (Appendix E) that represent all known agricultural use of chlorpyrifos in the United States.

Application scenario 1a. Representative maximum use rates for aerial application (liquids) are based on orchard crop use such as apples, nuts and citrus. Maximum allowable rate for citrus is limited to 3.5 lb a.i./acre. Aerial application of chlorpyrifos to orchards is limited to very unusual pest control situations, generally as a last resort due to wet conditions limiting utility of ground equipment. In most instances, the representative maximum use rate for orchard crops (2.0 lb a.i./acre) is also the typical use rate. Aerial application to orchards represents less than 1% of total chlorpyrifos applications to orchards (DAS marketing team input).

Applications to field crops represent the bulk of aerial applications of liquid formulations of chlorpyrifos. Primary field crops which utilize aerial applications of liquid formulations include cotton, wheat, alfalfa, sorghum, corn, sugar beets and soybeans. About 20% of applications of liquid chlorpyrifos to cranberries are aerially applied (personal communication, The Cranberry Institute). Cranberries have a maximum label use rate of 1.5 lb a.i./acre and a typical use rate of 1.0 lb a.i./acre. Maximum and typical aerial use rates for field crops that represent 99% of aerial applications of liquid chlorpyrifos are listed in the following table:

Maximum and Typical Aerial Use Rates of Chlorpyrifos on Crops

Crop	**Maximum Label Rate (lbs. a.i./A)**	**Typical Use Rate (lbs. a.i./A)**
alfalfa	1.0	0.75
corn	1.5	1.0
cotton	1.0	0.75
sorghum	1.0	0.75
soybeans	1.0	0.5
sugar beets	1.0	1.0
wheat	0.5	0.5

Application scenario 1b. Liquid chlorpyrifos formulations have representative maximum rates of 1.5 lb a.i./acre for groundboom applications and a maximum labeled rate for groundboom application of 5.0 lb a.i./acre as a pre-plant soil application to tobacco. This 5.0 lb a.i./acre maximum labeled rate on tobacco is only labeled for use to control nematodes in the states of

North Carolina and South Carolina, and currently has limited utility. However, a groundboom use rate of 2.0 lb a.i./acre is typically used as a pre-plant soil treatment for both tobacco and sweet potatoes. Maximum acres of tobacco and sweet potatoes annually treated with chlorpyrifos represent 139,000 acres, 1.3% of a maximum total of 10,506,000 acres of crops annually treated with chlorpyrifos.

The bulk of groundboom applications of liquid formulations of chlorpyrifos are made as foliar applications to field crops and directed applications to orchard floors. Maximum and typical groundboom use rates for crops that represent 99% of groundboom applications of liquid chlorpyrifos are listed in the following table:

Maximum and Typical Groundboom Use Rates of Chlorpyrifos on Crops

Crop	**Maximum Label Rate (lbs. a.i./A)**	**Typical Use Rate (lbs. a.i./A)**
alfalfa	1.0	0.75
Brassica (soil)	2.25	2.0
corn	3.0	1.0
cotton	1.0	0.75
mint	2.0	2.0
onions	4.0	2.0
orchard floors	4.0	2.0
sorghum	1.0	0.75
soybeans	1.0	0.5
sugar beets	1.0	1.0
sweet potatoes	2.0	2.0
tobacco	5.0	2.0
wheat	0.5	0.5

Application scenario 1c. Representative maximum use rates for airblast application (liquids) are based on orchard crop use such as apples, nuts and citrus. Maximum allowable rate for citrus is 6.0 lb a.i./acre. Over 70% of the foliar use of chlorpyrifos on citrus occurs in the San Joaquin Valley of California for control of California red scale at 6.0 lb a.i./acre. With the exception of citrus, the representative maximum use rate for orchard crops (2.0 lb a.i./acre) is also the typical

use rate. Airblast application represents greater than 99% of total chlorpyrifos foliar applications to orchards.

Maximum and typical airblast application use rates for crops that represent 99% of airblast applications of liquid chlorpyrifos are listed in the following table:

Maximum and Typical Airblast Application Use Rates of Liquid Chlorpyrifos on Crops

Crop	**Maximum Label Rate (lbs. a.i./A)**	**Typical Use Rate (lbs. a.i./A)**
almonds	2.0	2.0
apples/pears/stone fruit (dormant)	3.0	2.0
citrus	6.0	6.0
Christmas trees	1.0	1.0
grapes (dormant)	2.0	2.0
filberts	2.0	2.0
pecans	2.0	1.0
walnuts	2.0	2.0

Application scenario 2a. The WP formulation is sold only as an WSP formulation. Representative maximum use rates for aerial application of WP are based on orchard crop use such as apples, nuts and citrus. Maximum allowable aerial rate for citrus is limited to 3.5 lb a.i./acre. As was the case for liquid formulations of chlorpyrifos, aerial application of WP formulations of chlorpyrifos to orchards is limited to very unusual pest control situations generally as a last resort due to wet conditions limiting utility of ground equipment. In most instances the representative maximum use rate for orchard crops (2.0 lb a.i./acre) is also the typical use rate. Aerial application to represents less than 1% of total WP chlorpyrifos formulations applications to orchards.

Foliar applications to vegetable crops represent the bulk of aerial applications of WP formulations of chlorpyrifos. Primary vegetable crops that utilize aerial applications of WP formulations include broccoli, cauliflower and cabbage. The maximum use rate for aerial application to vegetable crops is 1.0 lb a.i./acre and this would also represent the typical use rate.

Lorsban 50W in Water Soluble Packets insecticide is not labeled for application through any type of chemigation system.

Application scenario 2b. The WP formulation is sold only as a WSP formulation. Representative maximum use rates for groundboom applications of WP formulations of chlorpyrifos are based on vegetable crop applications such as brassica. Primary vegetable crops that utilize groundboom applications of WP formulations include broccoli, cauliflower and cabbage. The maximum use rate for groundboom application to vegetable crops is 1.0 lb a.i./acre and this would also represent the typical use rate.

Application scenario 2c. The WP formulation is sold only as a WSP formulation. Representative maximum use rates for airblast application of WP formulations are based on orchard crop use such as apples, nuts and citrus. Maximum allowable rate for citrus is 6.0lb a.i./acre. Over 70% of the foliar use of chlorpyrifos on citrus occurs in the San Joaquin Valley of California for control of California red scale at 6.0 lb a.i./acre. With the exception of citrus, the representative maximum use rate for orchard crops (2.0 lb a.i./acre) is also the typical use rate. Airblast application represents greater than 99% of total chlorpyrifos WP formulations applied to orchards.

Maximum and typical airblast application use rates for crops that represent 99% of airblast applications of WP chlorpyrifos are listed in the following table:

Maximum and Typical Airblast Application Use Rates of WP* Chlorpyrifos on Crops

Crop	**Maximum Label Rate (lbs. a.i./A)**	**Typical Use Rate (lbs. a.i./A)**
almonds	2.0	2.0
apples	1.5	1.5
cherries, sour	1.5	1.5
citrus	6.0	6.0
filberts	2.0	2.0
pecans	2.0	1.0

walnuts	2.0	2.0

*Based on Lorsban 50W in Water Soluble Packets, EPA Reg. No 62719-221

Application scenario 3a. Representative maximum use rates for aerial application of Lorsban 15G insecticide are based on use in peanuts; that is also the maximum labeled rate. Aerial application of Lorsban 15G to peanuts is limited to very unusual pest control situations, generally as a last resort due to wet conditions limiting utility of ground equipment. Aerial application of Lorsban 15G to corn represents the common aerial application scenario. Maximum aerial use rate is 1.0 lb a.i./acre which is also the typical aerial application rate.

Application scenario 3b. Representative maximum use rates for ground application of Lorsban 15G insecticide should be based on 2.0 lb a.i./acre application rate to peanuts and the maximum use rate of 3.0 lb a.i./acre based on broadcast use in tobacco. Broadcast applications of 3.0 lb a.i./acre of Lorsban 15G to tobacco are highly uncommon since liquid formulations are preferred from both an economic and convenience perspective. In fact, broadcast applications of Lorsban 15G to all labeled crops represent less than 1% of the total volume of use in the United States. Typical use of Lorsban 15G as a ground application is 1.0 lb a.i./acre applied to corn as an at-plant T-band that represents >90% of all Lorsban 15G used in the United States.

Application scenarios 4a, 4b, 4c. There are no commercially available dry flowable chlorpyrifos products available in the United States.

Aerial (spray) – enclosed cockpit – scenario 5a. Comments on aerial use are the same as for application scenario 1a.

Aerial granulars – enclosed cockpit – scenario 5b. Comments on aerial use are the same as for application scenario 3a.

Groundboom tractor – scenario 6. Comments on groundboom use are the same as for application scenario 1b.

Airblast applicator – scenario 7. Comments on airblast applicator use are the same as for application scenario 1c.

Tractor-drawn granular spreader – scenario 8. Comments on tractor-drawn use are the same as for application scenario 3b.

Seed treatment – scenario 9. Lorsban 50-SL specialty insecticide is labeled only for use in commercial seed treating operations and only as a pre-plant slurry treatment of bean, corn, cucumber and pumpkin seeds to protect germinating seeds and seedlings from injury by seed corn maggots and seed corn beetles, and to protect stored seeds from injury by stored product insects. In this operation, 2 oz (0.0625 lb a.i.) of Lorsban 50-SL is mixed with water and 0.5% by weight methylcellulose (or another sticking agent) and in a volume adequate to thoroughly coat 100 lb of seed in a rotating blender. Typically, 12-15 oz of solution is required per 100 lb of seed.

Dip application (pre-plant peaches) – scenario 10. Lorsban-4E insecticide is labeled as a pre-plant dip application for non-bearing peach trees at the application rate of 3 qt (3.0 lb a.i.) per 100 gallons of water for control of peach tree borer. This involves the dipping of bare root seedling trees prior to planting in the orchard. The dip solution is typically diluted in an open tank and the bare root trees are dipped into the solution several inches above the grafting bud scar and then allowed to air dry before being moved to the field and planted. This operation can occur at the nursery that produces the bare root trees prior to sale to a grower who is establishing a new orchard, or the grower can perform the task at the site of the new planting. In either situation it is important to understand that the dipping operation occurs over a very short period of period. A nursery's entire inventory of bare root stalk can be treated within a period of less than one week.

_____. Comments on aerial use are the same as for application scenario 1a.

Granular applications – scenario 12. Comments on aerial use are the same as for application scenario 3a.

No comments for scenarios 13, 14, 15 and 16.

Page 7. DAS feels the appropriate endpoints and uncertainty factors should be based on human testing data. The following table presents those values which DAS feel are correct for assessment of occupational risk.

Table 2. Chlorpyrifos Hazard Endpoints and Uncertainty Factors

Route/ Duration	NOAEL (mg/kg/day)	Effect	Study	Uncertainty Factors[b]	Comments
Short-term Dermal	0.5	RBC cholinesterase inhibition at mg/kg/day		Intra species: 10x	3 percent dermal absorption.
Intermediate-term Dermal	0.1	RBC cholinesterase inhibition at mg/kg/day		Intra species: 10x	3 percent dermal absorption.
Short- and Intermediate-term Inhalation	Assessed at the NOEL appropriate for the term of work function.	Inhalation would be assessed at 100 % absorption and evaluated against the NOEL of concern since they are both based on oral dosing studies.			

Pages 41-49, Appendix A. DAS replaced the NOEL value for the short-term assessments presented in Appendix A with the DAS suggested value based on human testing, and used the EPA spreadsheet with the formulas and other parameters left as the Agency produced them. The results are presented as Appendix E to this document. Most of the scenarios had acceptable MOEs at Max PPE and all did with the Engineering controls.

Pages 50-63, Appendix B. Similarly, the animal-based NOEL was replaced with a human-based NOEL and the interim term assessments calculated via the EPA spreadsheet. Again, most scenarios exceeded the needed MOE of 10 for the Max PPE, and all but two did for the Engineering controls calculations. These tables are presented in Appendix E.

Page 51, Table B1, Scenario 2a. Apparently, there was a transcription error in bringing data from the calculation spreadsheet into Table B1.

	Daily Dose (mg/kg/day)	MOE	Daily Dose (mg/kg/day)	MOE	Total MOE
Currently Reads	0.12	0.3	0.26	0.4	0.2
Should Read	0.02	1.5	0.04	2.3	0.9

Page 54, Table B1, Scenario 14, all uses. Apparently, there was a transcription error in bringing data from the calculation spreadsheet into Table B1.

	Daily Dose (mg/kg/day)	MOE	Daily Dose (mg/kg/day)	MOE	Total MOE
Currently Reads	0.0044	7	0.0052	19	5
	0.0085	4	0.010	10	3
	0.0093	3	0.011	9	2
	0.017	2	0.020	5	1
Should Read	0.00026	113	0.00014	700	98
	0.00051	59	0.00027	360	50
	0.00056	54	0.00030	330	46
	0.000101	30	0.00055	180	25

2. Comments Pertaining to Occupational/Residential Handler and Postapplication Residential Risk Assessment for Chlorpyrifos Dated June 30, 1999

DAS' review of the "Occupational/Residential Handler and Postapplication Risk Assessment for Chlorpyrifos" for uses on turfgrass such as lawns and golf courses and also for retail

indoor/outdoor applications highlights a number of EPA errors, significant issues in how the risk assessments were conducted, and assumptions used regarding product use and the marketplace.

- For many of the products mentioned in this section, EPA did not include a registration number in their HED chapter, or included a registration number but no tradename, or in the case of granule baits provided no reference at all. Therefore, DAS had to use EPA's Pesticide Product Label System (PPLS) database to obtain the registration numbers by tradename, tradename by registration number, or by deduction. Since not all of the labels referenced in EPA's chapter were 100% identifiable, DAS was only able to comment on errors based on the assumption that the products used by the Agency in risk assessments were corectly identified.
- In the risk assessments conducted by EPA, product use inputs were often taken from insecticide generic use databases or extrapolated from crop or agricultural use scenarios. In many cases, these are not accurate or applicable scenarios for the typical use of chlorpyrifos and the risk assessments derived from these assumptions overestimate the actual risk in the marketplace. To help provide a better understanding of actual chlorpyrifos urban pest market usage and allow more refined assessments, DAS commissioned a small qualitative market research study by Mar-Quest in 1999. The information from this survey can be used to further advance risk assessments for these uses. DAS has provided the results of the survey with this response. DAS recognizes the challenges of interpreting the many varied uses in this market and offers our assistance to the Agency in analyzing and understanding existing labels, typical use patterns, and the survey data in more detail.
- DAS' ability to comment on errors was hampered by the lack of specific use scenario assumptions in the HED chapter, which were used as input parameters in the risk assessments. There were many references to the draft residential standard operating procedures (SOP), Pesticide Handlers Exposure Database (PHED), and HED/OPP assumptions. Even when these documents could be consulted it was often not clear what was being used to represent the picture of use for chlorpyrifos in the marketplace. The draft SOPs cited are still in the formative, draft stages and have not received final approval as indicated by the "do not quote or cite" precaution in the footnote of the SOP document. Since the SOPs are still being

validated and finalized, they should be used carefully and only in instances where there is a high degree of confidence in their accuracy and applicability. DAS requests EPA indicate any assessments conducted using these SOPs are based on procedures not yet validated or finalized and then provide new assessments once the SOPs are final. DAS also has an immediate concern that the draft SOPs indicate they do not include adjustments for exposure reduction techniques or specialized packaging that reduces exposure. Use of these SOPs, then, may greatly overestimate actual exposures for those chlorpyrifos products that have unique packaging, formulations, or PPE requirements. DAS requests the Agency consider these exposure reduction practices in their assessments to provide more realistic estimates of exposure and risk for both typical and maximum use scenarios.

- EPA also ran a number of risk assessments on product use scenarios that are inaccurate reflections of actual use in the marketplace, thus generating exposure scenarios that do not truly reflect actual risk. Examples include a risk assessment for use of chlorpyrifos by lawn care operators (LCO) which confused the perimeter treatment use directions for pest control operators, with the broadcast use directions for LCOs. Another example is where EPA referenced a draft SOP which indicates that one gallon of paint is needed to cover the average size bathroom -- and that this volume is therefore typical for brush-on applications of chlorpyrifos -- as relevant to a brush-on application to wood for control of wood infesting insects. Actually, for brush-on treatments, DAS labels specify: "for treatment of **small areas**, apply by brushing or spraying the diluted spray evenly on wood surfaces." Painting all the walls of a bathroom would exceed the definition of the small area treatment and would be inappropriate given the biology of wood infesting insects. A third example is where EPA assumed the volume of dust handled for chlorpyrifos was the same as that handled for carbaryl for use in vegetable gardens, even though our chlorpyrifos dust is not labeled for use on vegetables. These current risk assessments greatly overestimate the amount of material handled and, thus, overestimate exposure. DAS requests EPA conduct revised risk assessments to better refine actual exposure risk for these examples.

a. Non-Pest Control Operator Use

This portion of the response is relevant to non-WPS professional turf (i.e., lawn care, golf) and indoor/outdoor retail turf and ornamental markets by EPA chapter pages of the "Occupational/Residential Handler and Postapplication Risk Assessment for Chlorpyrifos" dated June 30, 1999. EPA has used the term pest control operaator (PCO) to also represent LCOs. In this response, DAS will refer to lawn care operators as LCOs, not PCOs, for purposes of clarification since these two market segments are often very different and distinct. EPA text is noted in italic font, DAS response/comments are noted in non-italic font.

(1) Products and Uses

These comments pertain to the non-PCO uses mentioned in the document specific to the non-WPS professional turf (i.e., lawn care, golf) and indoor/outdoor retail turf and ornamental markets as referenced from the DAS labels of Dursban Pro specialty insecticide (62719-166), Dursban 2E specialty insecticide (62719-65), Dursban 1-D Insecticide (62719-54), Dursban Turf Insecticide (62719-35), Dursban 1-12 Insecticide (62719-56), and Dursban 1/2G Granular Insecticide (62719-14) mentioned in this EPA chapter. All of these DAS labels are being commercialized with the exception of Dursban Turf Insecticide, which is not sold. DAS proposes that risk assessments based on this product are therefore not reflective of current uses for this label. However, many of the use patterns on the Dursban Turf Insecticide label are also on other commercially available 4 lb a.i./gal labels in the marketplace. In addition, seven products included in the section review by EPA are not DAS registrations. These products are: Ortho Ant Stop 0.5% Chlorpyrifos; Rainbow Kofire Ant Killer; Ortho Lawn Insect Spray (239-2423); Mosquitomist One; granule baits; dog collar (45087-49); and, cat collar (4306-16). Since we are not the primary registrant, DAS cannot comment on which of the non-DAS labels are currently being commercialized. For many of these products mentioned above, EPA did not include a registration number in their HED chapter, or they included a registration number but no tradename. Therefore, DAS used EPA's PPLS database to obtain the registration numbers by tradename, tradename by registration number, or by deduction (i.e., Ortho Ant Stop should be registration number 239-2619 since this was the only Ortho RTU ant control product at 0.5%

chlorpyrifos that still has an active registration as noted in the PPLS database) (U.S. EPA, 1994). Rainbow Kofire Ant Killer was found to have the registration number 13283-17, Mosquitomist was 8329-24, 4306-16 has the tradename Sulfodene Scratchex Flea and Tick Collar for Cats and 45087-40 is Zema 11-Month Collar For Dogs. Granule baits could not be found at all to comment on since no tradenames or registration numbers were provided by EPA.

Since not all of the labels referenced in EPA's chapter were 100% identifiable, DAS can only comment at this time on the labels identified and mentioned above for the comment and error response period. If DAS has incorrectly interpreted that these labels are the ones used by EPA for this chapter, then DAS requests EPA provide registration numbers for all the labels referenced so DAS can comment correctly on errors pertaining to them. DAS recommends to EPA that any matters associated with the non-DAS labels be discussed directly with the primary registrants of these products in addition to DAS.

DAS professional turf (i.e., lawn care, golf) and indoor/outdoor retail turf and ornamental comments pertain to this chapter's professional turf and retail use charter, which include only uses on lawns, golf courses, indoors by homeowners and outdoors on turfgrass and ornamentals by homeowners.

In the preliminary assessments included in the EPA chapter, inputs were often taken from insecticide generic use databases or extrapolated from crop or agricultural use scenarios. To help provide a better understanding of actual chlorpyrifos urban pest market usage and allow more refined assessments, DAS commissioned a small qualitative market research study by Mar-Quest in 1999. The information from this survey can be used to further advance risk assessments for these uses. DAS has provided the results of the survey with this response and highlighted selected results where applicable. DAS recognizes the challenges of interpreting the many varied uses in this market, and offers assistance to the Agency in analyzing and understanding labels, typical use patterns, and the survey data in more detail.

Although the Mar-Quest study has a small number of surveys per market segment (i.e., 11-14), DAS is of the opinion that with very few exceptions the median and mean responses fairly represent what is believed to be typical use in the field given DAS's professional experience selling chlorpyrifos for over 30 years. DAS recognizes there was one question in the survey which was poorly designed and, thus, the answers obtained from the question are not used in our comments to EPA. This question was "What is your percent split in the use of the average rate versus the maximum rate per acre (or per 100 gallons) of chlorpyrifos or Dursban." Comments concerning this question were previously mentioned in this response.

(2) Specific Errors and Comments

Page 2. "*There are approximately 850 registered products containing chlorpyrifos on the market.*"

According to EPA's PPLS database from 1994, there are currently 2062 chlorpryrifos labels, of which only 737 are active, and thus available for commercial use (U.S. EPA, 1994). Of the 737 active labels, less than this are actually sold in the marketplace given our own experience of maintaining active labels but not commercializing them at this time.

"*In addition, it is used as a mosquitocide.*"

This should be adult mosquitocide. The Moquitomist One label says to not apply directly to water. Chlorpyrifos can be used as an adult control product by ULV thermal or non-thermal fog producing equipment only and is not labeled for use as a larvicide where direct treatment of water would be needed. In fact, our technical manufacturing use labels specify that DAS's chlorpyrifos is not allowed to be formulated for uses which include aquatic use, nor can any other company use chlorpyrifos for the development of such a product.

Page 3. "*Chlorpyrifos, O,O-diethyl O-(3,5,6-trichloro-2-pyridyl) phosphorothioate, is an insecticide formulated as a wettable powder (containing 50% a.i.), emulsifiable concentrates (41.5-42.8%), dust (containing 0.1-7% a.i.), granular (containing 0.075%-15% a.i.), bait (containing 0.5% a.i.), flowables (containing 30% a.i.), impregnated material (containing 0.5-*

10% a.i.), pelleted/tableted (containing 0.5-1.0% a.i.), pressurized liquids (0.9-3.8% a.i.), and microencapsulated (0.5-2.5% a.i.). Dow AgroSciences states that formulations with concentrations greater than one pound a.i. per gallon (approximately 13% a.i.) are sold only to pest control or turf and ornamental professionals. Lower concentrations are available to homeowners from other suppliers for over-the-counter purchase. Except aerosols, granules and dusts, all formulated end-use products for application are diluted in water to a concentration of 1 percent a.i. or less (Dow AgroSciences 1998)."

For DAS active end-use labels (not technical manufacturing use labels) specific to the charter of this chapter, which is for urban uses only, all of the above are correct except for: emulsifiable concentrates can be up to 4 lb a.i./gal (approx. 47% a.i.); dusts are up to only 1% a.i.; granular formulations can go up to 2.5% a.i. (15% a.i. is for Lorsban, which is a product used in agriculture and not urban markets); and, professional concentrate can be up to 20% a.i. for the microencapsulated product. All of these formulations are professionally used. However, depending on the concentration, dusts and granules are generally used more retail than professional. DAS does not have active labels for baits, flowables, pellets/tablets, impregnated materials, or pressurized liquids. In terms of end-use dilution rates, 0.5% is the typical rate used by homeowners indoors and around the home's perimeter for insect control with chlorpyrifos.

In the absence of data, the Draft Standard Operating Procedures (SOPs) for Residential Exposure Assessments (December 18, 1997) were used to estimate exposures."

The SOPs cited are still in the formative, draft stages and have not received final approval as indicated by the "do not quote or cite" precaution in the footnote. The Agency solicited input when the draft SOPs were released with the idea that the input would refine the SOPs and create a "living document." DAS has dedicated significant time and resources through involvement with ongoing task forces to develop data to support and/or refine the SOPs. These efforts include surveys conducted or being conducted by the Outdoor Residential Exposure Task Force (ORETF) and Indoor Residential Exposure Joint Venture (IREJV). The ORETF has commissioned Stanford University to do a large videotaping study which includes the behavioral activities of one- and two-year-old children as well as other ages up to 12 years. Additionally, Stanford University has, at the request of the ORETF, used the videotaping analysis techniques to

compare videotaped jazzercise routines to children's contact with lawn surfaces to evaluate transfer factors from the jazzercise studies relative to child activity patterns. Software which includes the algothrims from the SOPs and is based on Excel has been developed by the OP Case Study Group. These and other initiatives should make significant impact on the viability of the SOPs. However, since the SOPs are still being validated and finalized, they should be used carefully and only in instances where there is a high degree of confidence in their accuracy and applicability. DAS requests the Agency indicate any assessments conducted using these SOPs are based on procedures not yet validated or finalized, and then provide new assessments once the SOPs are final. DAS has an immediate concern that the draft SOPs indicate they do not include adjustments for exposure reduction techniques or specialized packaging that reduce exposure. Use of these SOPs then may greatly overestimate actual exposures from those chlorpyrifos products that have unique packaging, formulations, or PPE requirements. DAS requests the Agency consider these exposure reduction practices in their assessments to provide more realistic estimates of exposure and risk.

"*There is insufficient use information and exposure data to assess exposure resulting from use in vehicles (i.e., planes, trains, automobiles, buses, boats) and other current label uses such as treatment of indoor exposed wood surfaces, supermarkets, restaurants, theaters, furniture, and draperies. However, HED has concern for these uses based on the scenarios assessed within this document.*"

DAS recognizes this and, as indicated on page 2 of EPA's residential exposure chapter, DAS has agreed to work with EPA to develop policies regarding prohibiting use in inappropriate areas such as drapes and furniture. Although no use-specific data is currently available for such uses, we can infer potential exposure from other residential use patterns which indicate exposures are low.

Page 6. "*In the absence of chemical-specific data, PCO exposures were estimated using data from PHED or the Draft Residential SOPs. The PHED data used for the mixer/loader for lawn treatment, and granular bait application (hand, belly grinder and push-type spreader) scenarios are representative of the chlorpyrifos uses as the surrogate data were monitored for the same*

uses. In the absence of PHED data, (e.g., dust application) the Draft Residential SOP assumptions were used."

See previous comments relative to the Residential SOPs for page 4 of EPA's assessment (pp 116-117). DAS is not able to clearly comment on errors regarding the granule baits since it is uncertain if EPA is referring here to chlorpyrifos mixed with insect food sources made into a granule or just non-food (i.e., clay, corn cob, etc.) granular formulations of chlorpyrifos. From looking at the labels EPA has referenced in their chapter, the only mention of granules pertains to labels that are not baits. DAS does not have any labels for bait granule formulations of chlorpyrifos. DAS asks EPA for more definition to be able to respond to errors.

"*Due to an absence of chemical-specific homeowner applicator studies, the majority of residential applicator risks were estimated based on the data from the Draft Residential SOPs.*"

See previous comments relative to the Residential SOPs for page 4 of EPA's assessment (pp 116-117).

"*Aerial and ground-based fogger mosquitocide application*"

This should be "adult mosquitocide." DAS requests EPA include the term "adult" wherever they use the reference to the Moquitomist One label.

Page 7. "*The only scenario that resulted in a MOE consistently above 300 was from the aerial and ground-based fogger mosquitocide applications.*"

This should be "adult mosquitocide." DAS requests EPA include the term "adult" wherever they use the reference to the Moquitomist One label.

"In the absence of chemical-specific data, exposures were estimated based on data from the Draft Residential SOPs (i.e., indoor crack and crevice treatment, and pet collar uses), which are considered to result in high-end risk estimates. Scientific literature studies, the AgDrift Model and the Draft Residential SOPs were used to evaluate mosquitocide uses."

See previous comments relative to the Residential SOPs for page 4 of EPA's assessment (pp 116-117). Should be "evaluate adult mosquitocide."

No data are available to evaluate the postapplication residential exposures and risks associated with the use of insecticidal dust products indoors. In addition, there are no recommended procedures for evaluating these products in the Residential SOPs. Nevertheless, HED has concerns about the use of these products based on the very low MOEs (i.e., < 10) calculated using the Residential SOPs for residents or workers that could apply these products."

See previous comments relative to the Residential SOPs for page 4 of EPA's assessment (pp 116-117). If there are no recommended procedures for evaluating residential exposure to use of dust formulations, DAS requests EPA provide more explanation of their approach to assess exposure so that comments on errors can be made.

Page 10. "*There are approximately 850 registered products containing chlorpyrifos on the market. Registered uses include a wide variety of food, turf and ornamental plants, as well as indoor product uses, structural pest control, and in pet collars. It is used in residential and commercial buildings, schools, daycare centers, hotels, restaurants, hospitals, stores, warehouses, food manufacturing plants and vehicles. In addition, it is used as a mosquitocide.*"

According to EPA's PPLS database from 1994, there are currently 2062 chlorpyrifos labels of which only 737 are active and, thus, available for commercial use (U.S. EPA, 1994). Of the 737 active labels, less than this are actually sold in the marketplace given our own experience of maintaining active labels but not commercializing them at this time. Also, mosquitocide should be adult mosquitocide.

"*Chlorpyrifos, O,O-diethyl O-(3,5,6-trichloro-2-pyridyl) phosphorothioate, is an insecticide formulated as a wettable powder (containing 50% a.i.), emulsifiable concentrates (41.5-42.8%), dust (containing 0.1-7% a.i.), granular (containing 0.075%-15% a.i.), bait (containing 0.5% a.i.), flowables (containing 30% a.i.), impregnated material (containing 0.5-10% a.i.), pelleted/tableted (containing 0.5-1.0% a.i.), pressurized liquids (0.9-3.8% a.i.), and microencapsulated (0.5-2.5% a.i.). Dow AgroSciences states that formulations with concentrations greater than one pound a.i. per gallon (approximately 13% a.i.) are only to pest control or turf and ornamental professionals. Lower concentrations are available to*

homeowners from other suppliers for over-the-counter purchase. Except aerosols, granules and dusts, all formulated end-use products for application are diluted in water to a concentration of 1 percent a.i. or less (Dow AgroSciences 1998)."

For DAS active end-use labels (not technical manufacturing use labels) specific to the charter of this chapter, which is for urban uses only, all of the above are correct except for: emulsifiable concentrates can be up to 4 lb a.i./gal (approx. 47% a.i.); dusts are up to only 1% a.i.; granular formulations can go up to 2.5% a.i. (15% a.i. is for Lorsban, which is a product used in agriculture and not urban markets); and, professional concentrate can be up to 20% a.i. for the microencapsulated product. DAS does not have active labels for baits, flowables, pellets/tablets, impregnated materials, or pressurized liquids. In terms of end use dilution rates, 0.5% is the typical rate used by homeowners indoors and around the home's perimeter for insect control with chlorpyrifos.

Page 11. "*Handgun (PCO): Broadcast turf application*"

Should read "Handgun (LCO): Broadcast turf application." Professional applicators for the lawn care industry are called LCOs, which stands for lawn care operators, instead of PCO, which refers to pest control operators that service the pest control and not lawn care market segments. In this response, DAS will refer to lawn care operators as LCOs, not PCOs, for purposes of clarification since these two market segments are often very different and distinct.

Page 12, 26. "*It is important to note that most individuals in the U.S., and nearly all the subjects in the Dow AgroSciences biomonitoring studies had low levels of urinary 3,5,6-TCP prior to study commencement, indicating a baseline exposure to chlorpyrifos, which most likely is attributed dietary sources.*"

See section on Biomonitoring in the DAS response on page 158.

Page 13. "*The baseline clothing/PPE ensemble for occupational exposure scenarios is generally an individual wearing long pants, a long-sleeved shirt, no chemical-resistant gloves (there are exceptions pertaining to the use of gloves and these are noted), and no respirator.*"

Of the turf and ornamental labels referenced in this EPA chapter that are occupationally used, in addition to that considered as baseline PPE, Dursban Pro specialty insecticide also requires the use of chemically resistant gloves and footwear. DAS requests EPA use the label-mandated PPE requirements as the basis for their baseline PPE scenario and rerun their assessments to better determine actual exposure risk. By not including all of the label mandated product specific PPE into their baseline PPE scenarios, these assessments overestimate exposures for these products.

Page 15. "*It was assumed that a residential applicator would wear short-sleeves, short pants and no gloves, that an average applicator weighs 70 kg, and applies the entire contents of a 16 ounce aerosol can that contains one percent ai chlorpyrifos (w/w, 0.16 oz or 4.5 g).*"

Based on discussions with formulator customers that service the retail marketplace, the typical concentration of chlorpyrifos in an aerosol formulation is 0.5%. The typical use of an aerosol can of chlorpyrifos is to apply 2 oz during each application (not an entire 16 oz can) at approximately 30-day intervals eight times a year. This then results in 0.0006 lb a.i. handled and not 0.01 lb as used by EPA in their risk assessment. The product EPA references in their chapter to represent a chlorpyrifos labeled aerosol product has a 0.5% concentration (as deduced by DAS, this product is Ortho Home Defense Hi-Power Brand Roach, Ant and Spider Killer registration number 239-2619). DAS requests EPA reassess exposure using the more typical concentration for an aerosol can and the more typical use scenario, and then update Table 2 to represent the output of the revised risk assessment. In addition, EPA's assessment relied on use pattern information contained in the draft SOPs which are not finalized. Due to both of these factors, these current risk assessments may greatly overestimate the typical, actual risk.

Page 17. "*The applications used in this study deviated slightly from those recommended by the label, and are likely to underestimate exposure. For example, the label recommends using 0.03 to 0.12% for high volume broadcast sprays at a rate of 10 gallons/1000 ft^2, whereas, the exposures from this study were based on 0.12% applied at 2 gallons/1000 ft^2. The label recommends that higher concentrations of 0.5% chlorpyrifos be applied using low volume sprays (i.e., 2 gallons /1000 ft^2). Therefore, it is possible that this study underestimates the actual exposures to PCOs following the label recommendations for broadcast treatment (i.e., the study*

The above statement for use of chlorpyrifos by LCOs for broadcast treatment of turfgrass for insect control is intermingled with the label recommendations designed for PCOs that make perimeter treatments and not broadcast treatments to turfgrass. The Dursban Pro specialty insecticide label is split into two sections to represent the marketplace -- pest control and turf and ornamental care. The turf and other outdoor uses section of the label allow for chlorpyrifos to be applied from 1-4 lb a.i./acre as a broadcast treatment to turfgrass. In order to get to percent concentration values of the spray material, one needs to be aware of the spray volumes used per acre to control different types of pests. For example, for control of surface feeding insects, LCOs generally apply 2 gal/1000 sq ft (87 gal/acre) of dilute spray. The typical labeled use rate for surface feeders is 1 lb a.i./acre (Mar-Quest, 1999). So, if one applies 1 lb a.i. in 87 gallons of water onto one acre, then the percent concentration of the spray is 0.13% which is what was used in the design of the exposure study and represents the typical scenario of chlorpyrifos use by LCOs. For control of subsurface feeding insects, the volume used is 4 gal/1000 sq ft (174 gal/acre).

The section of the label that is called “general pest control – perimeter treatments” is specific to PCOs making perimeter treatments and not broadcast applications to entire lawns. Since state regulatory agencies require training and certification specific to pesticide use as a PCO separate from an LCO, it is thus extremely rare that one company would have applicators carrying dual certifications to be able to serve both industries. This PCO (not LCO) section of the label says to use 0.03-0.12% as the dilution concentration and then apply using 10 gal/1000 sq ft, 2-3 feet up the base of the structure’s foundation and to treat a band of soil around the structure out to a distance of 6-10 feet. This high volume spray of 10 gal/1000 sq ft is not labeled for broadcast application to turfgrass, but is specific to perimeter treatment around a structure where there are often thick layers of mulch and other organic matter that needs to be penetrated to control the

insects that reside deep in this type of harborage. The high concentration (0.5%) in a low volume spray is specific to the perimeter section of the label where the label specifically states this is for treatment of cracks and crevices along walkways, patios, windows, and door frames or other areas where insects may congregate or can gain entrance to the structure. Use on turfgrass is never mentioned.

DAS requests EPA separate the perimeter use information from the lawn care use information and rerun their risk assessment to be able to accurately reflect the true exposure specific to lawn care applicators, and then update Table 2 to represent the revised output of this new assessment.

The Mar-Quest research study is provided to EPA to aid in updating the use information in EPA's Table 3 and for incorporation into risk assessments for the typical use scenarios specific to chlorpyrifos for the turf and ornamantal market segments for this chapter. DAS requests EPA incorporate this chlorpyrifos specific information into their risk assessment revisions. The Executive Summary is provided in Appendix E, and the full report will be submitted with this document.

Page 17. "*Because the biomonitoring study did not evaluate exposures for mixer and loading activities, these scenarios were evaluated using PHED V1.1. Three unit exposures for a mixer/loader handling liquid were evaluated and are presented in Table 2. One for baseline (no PPE), another for a single layer of clothing and gloves, and the third for two layers of clothing and gloves.*"

The baseline no PPE scenario is not applicable since the Dursban Pro specialty insecticide label does specify to use eye protection and chemically resistant gloves when handling concentrate.

"*HED has no data monitoring chlorpyrifos exposures to residents during broadcast or spot treatment of turf. Therefore, exposures were evaluated based on data obtained from the Residential SOPs (also from PHED V1.1) for mixing/loading and application activities.*"

See previous comments relative to the Residential SOPs for page 4 of EPA's assessment (pp 116-117).

"*For the broadcast treatment, it was assumed that a resident would use a hose end sprayer to treat 0.5 acre/day of turf.*"

The typical size lawn is 15,000 sq ft; this should be used in the risk assessment to better represent the typical scenario (National Gardening Association, 1997-1998). DAS requests EPA rerun their risk assessments to reflect use on 15,000 sq ft instead of their 21,780 sq ft originally used, and then update the information in Table 2 using the new output of the risk assessment.

Page 18. "*The label recommends diluting 3-12 oz of Dursban 1-12 Insecticide (12.6% ai; 1 lb ai/gallon) with1 to 3 gallons of water. As shown on Table 2, a range of dose estimates were calculated for broadcast treatment, assuming application at both the minimum and maximum dilution rates of 3 to12 oz/gallon/ water/ 1000 ft^2 … For spot treatment, the maximum application rate of 12 oz ai/gallon water 1000 ft^2 resulted in short-term dermal and inhalation doses of 134 and 0.04 µg/kg/day, respectively. These short-term dermal and inhalation dose estimates are presented on Table .2*"

DAS requests EPA also run risk assessments to reflect the minimum rate use scenario for the spot treatment use as was done for the broadcast use, and add this information to Table 2. Given input from formulator customers, homeowners typically apply the 1 lb a.i./acre rate, which for Dursban 1-12 Insecticide is the 3 oz/gal dilution. The current assessment for this use overestimates the exposure risk for the way the product is used the majority of the time in the marketplace. In addition, the 1000 sq ft assumption EPA uses in their draft SOPs to represent total area sprayed for spot treatment applications seems excessive since this represents up to 7% of the total lawn area of the typical 15,000 sq ft lawn.

Page 19. "*These dose estimates represent a central-tendency to high-end scenario for residential applicators, who are more likely to apply one can of product rather than the five cans used in the study, but could wear shorts rather than long pants. These dose estimates represent a reasonable scenario for a commercial applicator because even though the volunteers wore short-sleeves and no gloves, PCOs would presumably be applying the product more than one hour/day*."

DAS agrees with EPA that homeowners would apply less than five cans per day (120 oz) as used in this study. In fact, given our experience and from discussions with formulator customers, homeowners typically apply 0.25 gallons (32 oz) of a ready to use (RTU) 0.5% chlorpyrifos product. In terms of PCO exposure, although it is possible that a PCO could use an RTU product, this is an extremely rare event. Almost all PCOs will purchase concentrates since this is more economical for them, or if an RTU formulation is desired, this is usually an aerosol formulation and not an RTU end use dilution. PCOs wear long sleeves and would rarely be seen wearing short-sleeved shirts during the job. If a PCO exposure scenario is to be determined, extrapolation from the homeowner scenario is not completely appropriate, and DAS requests EPA conduct a risk assessment specific to PCOs. However, even such an assessment would not be marketplace applicable since PCOs refrain from using RTU liquids.

For the risk assessment run by EPA, DAS cannot comment on errors since EPA has provided no information or even a reference to their assumptions regarding product use. DAS requests EPA provide this information so that we may comment on errors.

"*HED has no data monitoring exposures from chlorpyrifos application using a duster. This scenario was evaluated using two methods. First, the residential SOPs were used to evaluate this exposure scenario for both residential applicators (handling dust products that contain 1% ai) and utility workers (i.e., during application of product to underground wires or cables) that could handle a more concentrated product (7% ai, EPA Reg 13283-17). The Residential SOPs recommend that 10% of ai is available for dermal and inhalation exposure to applicator. It was assumed that dermal exposure contributed 99% to the total exposure, while inhalation contributed only 1% based on the relative exposure estimates for a wettable powder during open mixing and loading from PHED V1.1.*"

See previous comments relative to the Residential SOPs for page 4 of EPA's assessment (pp 116-117). DAS's dust labels only go up to 1% a.i. DAS professional use chlorpyrifos wettable powder formulations are all packaged in water soluble bags and, thus, bridging from assumptions for wettable powder mixing and loading exposure to use of a dust formulation is not applicable. In addition, dust formulations available to the retail consumer are generally packaged in a fiber

can with a perforated lid to be used as a shaker container. There is no mixing or measuring required so exposure here as a result should be non-existent other than via the application route.

"*In addition, exposures were derived from 24 replicates obtained from a study in the scientific literature (Kurtz and Bode 1985) in which a dust formulation was applied to a home garden. (This analysis is presented in memo from D. Jaquith to Chlorpyrifos file, June 11, 1996 entitled Documentation of Applicator Exposure Assessment for Chlorpyrifos Reregistration Eligibility Document--Application in the Residential Environment). An assumption of 0.02 lbs ai was used based on the amount of dust handled in each 15 minute replicate. The dose estimates for chlorpyrifos were derived from a surrogate study in which a 5 percent carbaryl dust was applied using a shaker can to corn and beans in a residential. This is conservative for chlorpyrifos because most of the dust products contain 1% or less of chlorpyrifos. Only one product (Rainbow Kofire Ant Killer) intended for commercial use contains 7% chlorpyrifos.*"

The use of these surrogate studies greatly overestimates the risk to homeowners applying chlorpyrifos dust products since DAS does not have any labels that allow for use of a dust on vegetables. Dust use in a vegetable garden would generally be much higher volume than that used for general pest control in and around the house. The DAS 1% dust label is written for use as spot treatments in and around the home with a volume of use recommended to be 1/3 to 2/3 oz of dust per square yard of spot treatment area. DAS requests EPA revise their risk assessment to accommodate this lower use volume and update their Table 2 with the new risk assessment output. In addition, in Table 2 for this use for both homeowners and workers, EPA references the draft SOPs. See comments above relative to the Residential SOPs for page 4 of EPA's assessment. DAS cannot comment on errors since assumptions specific to dust use could not be found in the draft SOPs or in the HED document.

Page 20. "*HED has no data monitoring exposures from chlorpyrifos application of granular bait by hand. Therefore, exposures were evaluated based on data obtained from PHED V1.1. for PCOs, and the Residential SOPs for residential applicators (also from PHED V1.1)… It was assumed that an average application dispensed is 0.97 lbs of active ingredient. This was the average amount of active ingredient handled in the 55 replicates for application of granular bait in the studies cited in PHED.*"

DAS does not have any non-manufacturing use labels for chlorpyrifos as a granule bait for control of insects. See comments above relative to the Residential SOPs for page 4 of EPA's assessment. DAS cannot comment on errors for this use since EPA does not reference the use of any chlorpyrifos label for a bait type formulation. Granular bait type formulations are generally applied as spot treatments or in a barrier around structures. Simply assuming 0.97 lb a.i. exposure from the exposure study conducted as the amount of exposure that would occur in the marketplace without knowledge of the use instruction on the label for such a product may either under or overestimate actual risk. DAS requests EPA find an active registration for a chlorpyrifos bait formulation and run their risk assessment on the exposure potential as reflected in the use direction for such a product. Once the risk assessment has been revised to reflect a labeled use then DAS also requests EPA update the content of their Table 2. Chlorpyrifos bait formulations exist for control of fire ant mounds from formulators. Such products are applied directly to the fire ant mound and are not broadcast onto the lawn.

Page 21. "*HED has no data monitoring exposures from chlorpyrifos application of granular bait using a belly-grinder. Therefore, exposures were evaluated based on data obtained from PHED V1.1. for PCOs, and the Residential SOPs for residential applicators (also from PHED V1.1)…Similar to the scenario discussed above, it was assumed that an average application dispensed is 0.97 lbs of active ingredient. This was the average amount of active ingredient handled in the 55 replicates for application of granular bait in the studies cited in PHED.*"

See previous comment directly above. Granular bait type formulations are generally applied as spot treatments or in a barrier around structures. In order to make such applications a belly-grinder is not used since this type of equipment is designed for broadcast treatment of areas such as turfgrass and is not optimized to make spot treatment or perimeter applications.

"*HED has no data monitoring exposures from chlorpyrifos application of granular bait using a push-type spreader. Therefore, exposures were evaluated based on data obtained from PHED V1.1. for PCOs, and the Residential SOPs for residential applicators (also from PHED V1.1). Similar to scenario discussed above, it was assumed that an average application dispensed is 0.97 lbs of active ingredient. This was the average amount of active ingredient handled in the 55 replicates for application of granular bait in the studies cited in PHED.*"

See previous two comments directly above. Granular bait type formulations are generally applied as spot treatments or in a barrier around structures. In order to make such applications a push-type spreader is not used since this type of equipment is designed for broadcast treatment of areas such as turfgrass and is not optimized to make spot treatment or perimeter applications.

For all three application scenarios for a granule bait, it is unclear if EPA is actually referring to granule bait formulations as they stipulate or actually intended to refer to non-bait granular formulations.

Page 25. "*HED has no data monitoring exposures to chlorpyrifos resulting from a paintbrush application to treat insect-infested wood. Therefore, exposures were evaluated based on data obtained from the Residential SOPs for residential applicators (also from PHED V1.1). These data represent a worker painting a bathroom with a fungicide-treated latex paint. PCOs were not evaluated for this scenario because they are assumed to treat larger surfaces of wood with rollers or a spray, rather than a paintbrush. For this scenario, it was assumed that an individual could apply one gallon of diluted chlorpyrifos product (as Dursban 1-12 Insecticide; EPA Reg No. 62719-56) to treat wood infested with insects. The label recommends diluting 5.33 oz of Dursban 1-12 Insecticide (12.6% ai; 1 lb ai/gallon) with 1 gallon of water*."

See previous comments relative to the Residential SOPs for page 4 of EPA's assessment (pp 116-117). It should also be noted DAS no longer allows chlorpyrifos to be incorporated into paint. The SOP section which references a worker applying a fungicide-treated latex paint represents that one gallon was used since this is the amount of paint needed to cover the average size bathroom from a cover-the-wall-with-a-color scenario (the fungicide is just along for the ride to control mold and mildew as the wall is being color painted). This type of broad paint-on use is not representative of the use of a dilution of chlorpyrifos where it is brushed on to susceptible wood for control of wood infesting insects. The Dursban 1-12 Insecticide label does recommend to use 5.33 oz/gal of water to treat wood either as a brush-on or spray-on treatment. Brush-on treatments are usually made as spot treatments to areas of wood where wood infesting insects are causing damage or have emerged from the wood. The Dursban 1-12 label specifically states: "for treatment of **small areas**, apply by brushing or spraying the diluted spray evenly on wood surfaces." Painting all the walls of a bathroom would exceed the definition of the small area

treatment. For treatment of large areas, such as bathroom walls, the label recommends using a spray. The current risk assessment greatly overestimates the amount of material handled for brush-on use and, thus, overestimates exposure risk. DAS requests EPA conduct a revised risk assessment recognizing the difference between these two application patterns. Once rerun, DAS requests EPA update Table 2 with the new assessment output.

"*HED has no data monitoring chlorpyrifos exposures to residents during mixing/loading or application to ornamentals (flowers, shrubs, evergreens, vines, shade and flowering trees and other ornamental plants). Therefore, exposures were evaluated based on data obtained from the Residential SOPs (also from PHED V1.1) for mixing/loading and application activities. This assessment evaluates application via both a low pressure handwand and a hose end sprayer, which are assumed to be short-term scenarios for residents. A range of exposure estimates were evaluated for both application methods, the minimum, typical and maximum dilution rates of 1 oz, 4 oz and 1 quart of product per 3 gallons of water. The maximum rate is recommended for beetles. It was assumed that a resident would apply 5 gallons of diluted Dursban 1-12 Insecticide (EPA Reg No. 62719-56; 12.6% ai; 1 lb ai/gallon), in accordance with the residential SOPs for treatment of ornamental trees.*"

See previous comments relative to the Residential SOPs for page 4 of EPA's assessment (pp 116-117). Although DAS does not have any data to further refine EPA's assumption of 5 gallons of dilution to treat ornamental trees, this volume does seem excessive from personal experience.

Page 28. "*The estimated doses for dermal and oral exposures are paresented in Table 3. As shown in the table, the estimated doses are signigicantly higher than those estimated from the biomonitoring study, suggesting that dermal and oral exposures are of concern in rooms treated with chlorpyrifos.*"

DAS disagrees with the interpretation of the difference between estimated exposures using default values and estimated exposures using measured doses. Although time was spent in rooms other than those treated, there was also significant time spent in the rooms treated in the biomonitoring study resulting in the measured dose for each participant. The biomonitoring measured dose does take into account dermal and oral exposures for the individuals monitored. Calculated exposures, which are significantly higher than measured doses, suggest the calculations have questionable inputs, not that the biomonitoring data do not measure oral and dermal exposures.

Page 30. "*HED has no chemical-specific data that evaluate exposures to individuals from the use of pet flea collar products. Therefore, HED conducted this analysis in accordance with HED's 1997 Draft SOPs for Residential Exposure Assessments.*

See previous comments relative to the Residential SOPs for page 4 of EPA's assessment (pp 116-117). It should be noted there is currently a pet collar exposure study being conducted at Mississippi State University by Dr. Janice Chambers.

Page 32. "*In addition, the exposures may be underestimated for individuals that follow the label because only 75% of the theoretical recommended label rate was applied to the field where exposure activity occurred.*"

The maximum rate for chlorpyrifos granules is 2 lb a.i./acre. If 1.8 lb a.i./acre was applied, then this represents 90% of the labeled rate and not the 75% mentioned by EPA.

Page 34. "*Average doses for adults are expected to range from 1.4 to 6.3 µg/kg/day for a 4 hour exposure the day of product application.*"

EPA draft SOPs indicate the exposure period to be two hours instead of the four hours used. This risk assessment should be corrected to incorporate the two-hour time period and the content of Table 3 updated.

Page 36. "*Because there is insufficient information to determine if lawn care professionals are exposed for intermediate (7 days- several months) or long-term durations, the long-term toxicity endpoints were conservatively used to calculate the MOEs based on the biomonitoring results for applicators.*"

The Mar-Quest study indicates LCOs are subject to intermediate-term exposure. They apply chlorpyrifos 5-30 times per year, depending on the formulation and pest category of surface or subsurface feeder (Mar-Quest, 1999).

Pages 35-43. These pages in EPA's report verbalize the output and interpretation of the risk assessments as run by EPA and repeats much of the same information already addressed in DAS' comments above. DAS requests EPA consider all of the above comments and incorporate them into their revision of the risk assessments to better refine the actual exposure risk in the marketplace. Doing so will yield new and more refined results which should be incorporated into a revision of the conclusion statements made on pages 35-43 and in Tables 2 and 3. DAS believes consideration of this additional information allows significant refinement of the risk assessments to more accurately reflect exposures and risk in the real world.

b. Professional Pest Control Operator Use

This response addresses the exposure assessments for non-WPS professionally applied structural (i.e., termiticide, wood destroying insects) and indoor/outdoor general pest control (cockroaches, ants, etc.) markets. Responses are presented by EPA chapter pages of the "Occupational/Residential Handler and Postapplication Risk Assessment for Chlorpyrifos" dated June 30, 1999. EPA text is noted in italic font, DAS' response/comments are noted in non-italic font.

(1) Products and Uses

These comments pertain only to the professional PCO uses mentioned in the document specific to the non-WPS professional structural (termite and other wood destroying insect treatments), indoor crack and crevice (cockroaches, ants, etc.) and outdoor perimeter pest (peridomestic cockroach, ant, etc.) applications, which are described on the DAS labels of Dursban TC specialty termiticide concentrate (62719-47), Equity* specialty termiticide concentrate (62719-167), and Dursban Pro specialty insecticide (62719-166). DAS' Response to EPA's draft science chapter text includes the following.

(2) Specific Errors and Comments

Pages 3, 10. "*Chlorpyrifos, O,O-diethyl O-(3,5,6-trichloro-2-pyridyl) phosphorothioate, is an insecticide formulated as a wettable powder (containing 50% a.i.), emulsifiable concentrates*

*Trademark of Dow AgroSciences LLC

(41.5-42.8%), dust (containing 0.1-7% a.i.), granular (containing 0.075%-15% a.i.), bait (containing 0.5% a.i.), flowables (containing 30% a.i.), impregnated material (containing 0.5-10% a.i.), pelleted/tableted (containing 0.5-1.0% a.i.), pressurized liquids (0.9-3.8% a.i.), and microencapsulated (0.5-2.5% a.i.)."

The reference to the maximum formulated microencapsulated product containing chlorpyrifos is incorrect. The maximum concentration should be 20% (Empire* 20, 62719-88).

Pages 4, 6, 7. "*In the absence of data, the Draft Standard Operating Procedures (SOPs) for Residential Exposure Assessments (December 18, 1997) were used to estimate exposures. Obviously, exposures associated with all uses of chlorpyrifos products have not been monitored. Therefore, the available data were used to evaluate similar uses (i.e., lawn studies used to evaluate yard and ornamental sprays, residential crack and crevice exposure data used to evaluate similar treatments in other buildings).*"

See previous comments relative to the Residential SOPs for page 4 of EPA's assessment (pp 116-117). A cursory review of this draft SOP identified a number of overly conservative estimates of the quantities of insecticides assumed to be applied by PCOs which were later used to drive a number of risk assessments. Where appropriate, DAS will comment on specific use patterns and offer information from a recent market research study (Mar-Quest, 1999) to further advance realistic risk assessments for these uses. Although this study is small in scope, DAS believes, with very few exceptions, the median and mean responses fairly represent what are believed to be typical use in the field given a professional experience of selling chlorpyrifos for over 30 years.

Page 6. "*Overall, the exposures and risks for PCOs based on the chemical-specific biomonitoring studies are considered to be central tendency estimates because they evaluated less than a full day's exposure at the maximum label rate or they exclude accidental exposure (e.g., exposure resulting from a broken hose).*"

DAS is puzzled that exclusion of an accidental exposure data point *(e.g., exposure resulting from a broken hose)* affects the quality of the remaining data points in a study. The accepted regulatory and scientific approach has been that assessments of applicator exposure should be designed to measure exposures for specific work functions accurately and should not be designed to assess accidental exposures.

Page 21. "*The M/L/A performed an open-pour mixing/loading task in which a PCO loaded Dursban® TC concentrate into a mixing tank containing the appropriate amount of water. After mixing, the diluted product was sprayed onto the tarp using a hand-held sprayer. After the termiticide was applied to the tarp, two workers (tarp pullers) laid the tarp over the excavated area where the concrete foundation was to be poured.*"

The statement that *the diluted product was sprayed onto the tarp using a hand-held sprayer* is incorrect. A pre-construction treatment is conducted by applying the diluted product to the soil, and then placing an untreated plastic tarp (to serve as a vapor barrier) over the treated soil prior to the pouring of a concrete slab.

Page 23. "*During mixing/loading, subjects wore additional PPE: chemically resistant footwear and an extra coverall or a chemically resistant apron (not required by the label).*"

The statement above is inaccurate. The additional PPE of *chemically resistant footwear and an extra coverall or a chemically resistant apron* are currently required on our Dursban TC specialty termiticide concentrate label, as per Pesticide Regulation Notice (PRN 96-7). The *chemically resistant apron* was added to the originally specified mixer-loader PPE as an option based on discussions with the EPA that this would be viewed as an acceptable option to the second set of coveralls during mixing.

Page 27. "*In conclusion, these data demonstrate that exposures to adults and children following crack, crevice and spot applications of chlorpyrifos in the kitchen and bathroom by a licensed applicator are comparable to typical background exposures levels. However, these data do not support the use of crack and crevice or spot treatment in bedrooms, living rooms, closets, day care centers, schools, playhouses, on furniture or draperies, or in other rooms that could result in higher exposure to individuals, particularly children.*"

It is important to note that while the label provides the flexibility for the PCO applicator to apply chlorpyrifos dilutions as a crack and crevice or spot treatment in a number of structural settings (i.e., kitchens, bathrooms, bedrooms, living rooms, day care centers, schools, playhouses, etc.), the actual treatment site(s) and amount applied would be governed by the target pest. The main

insect pest targeted during interior applications in residential settings is the German cockroach. German cockroaches are most likely to be found in cracks and crevices in kitchens and bathrooms (Appel and Reid, 1992), hence, most insecticide applications will be focused there. Ants, on the other hand, may be found adjacent to their entry points (such as around doors, windows, etc.), and in that regard would require crack and crevice or spot applications inside structures to be focused where the pests are found. This targeting is supported by a July 1999 market research study conducted by Mar-Quest, on behalf of DAS, which documented that in single family detached structures the median volume of chlorpyrifos applied as an interior crack and crevice or spot treatment was 0.25 gallons (Table 11 from Mar-Quest study).

This same market research study documented that in multi-family residential structures, the median volume of chlorpyrifos applied crack and crevice in all affected attached apartments within a multi-family structure was 2.0 gallons (Table 16 from Mar-Quest study). It is important to recognize that the average volumes provided by PCOs in this survey would certainly be impacted by the number of unspecified living units making up a typical single multi-family structure from their particular trade area (i.e., duplex, four-plex, or 20-40 apartments per building).

Pages 38-39. "***(9) Post-Construction Termiticide Treatment****. In addition, during mixing and loading the workers also wore a second layer of clothes or apron and chemically resistant boots (not required by the label).*"

The statement above is inaccurate. The additional PPE of *a second layer of clothes or apron and chemically resistant boots* are currently required on our Dursban TC specialty termiticide concentrate label, as per PRN 96-7. The *chemically resistant apron* is also specified on our current Dursban TC label and was tested in the study cited as an option to the second pair of coveralls during mixing.

Page 44, Table 2. The calculations for dermal dose lacks the application of the 0.03 dermal absorption factor for the long-term PCO with PPE scenario.

	Central Tendency Dose (µg/kg/day) (a)		MOE (b)		
	Dermal	Inhalation	Dermal	Inhalation	Total
Currently Reads	0.51	0.15	59	197	45
	0.005	0.0015	5900	20000	4500
	1.75	0.52	17	58	13
Should Read	0.0153		1960		179
	0.00015		200,000		18,000
	0.9525		570		53

c. Post-Application Exposure

There was insufficient information provided in the EPA HED document on post-application residential exposures to determine errors or re-create EPA's risk assessments. From the information provided by EPA, DAS was not able to determine which data values were used or how the risk assessments were calculated and, as a result, the EPA HED risk assessment for post-application residential exposure is not transparent. DAS requests that EPA provide detailed descriptions on how their risk assessments were conducted. The following is a summary of DAS points with regard to post-application residential exposure.

Human toxicological data should be used to determine the NOEL instead of animal data. Based on human data the NOEL is 0.5 mg/kg/day for acute and 0.1 mg/kg/day for chronic. The resulting acceptable MOE is 10, which represents the uncertainty for intraspecies. Since toxicological data does not indicate additional sensitivity to neonates under expected exposure and conditions, DAS maintains that an additional FQPA safety factor is not required for chlorpyrifos.

DAS has conducted example risk assessments for turf uses (both spray and granular), crack and crevice treatments, and termiticide treatments using the Residential Exposure Assessment Spreadsheet Tool (REx) developed by the OP Case Study Group. This exposure assessment tool is based on the algorithms and premise promulgated by the residential SOPs and uses Excel as the vehicle for calculation. The REx assessments are conservative since they represent single point estimates based on data generated by DAS. In addition, the data chosen represent the maximum concentrations found in a study, which further adds to the conservative nature of the DAS assessment. Ingestion of soil and formulated granules by children were not included in these assessments. The FQPA Implementation Working Group (IWG) submitted comments to the Agency pertaining to the Draft Standard Operating Procedures for Residential Exposure Assessments on March 5, 1999 (Comments by The FQPA Implementation Working Group). In this response the IWG states that "ingestion of formulated pesticide is more appropriately characterized as an episodic event." They propose that it should not be included in residential exposure assessments since the focus of these exposure assessments is on anticipated, routine daily exposure pathways such as dermal contact with floor surfaces. The acute toxicological endpoint used in these assessments was 0.5 mg/kg/day. In order to maintain transparency in the risk assessment process, the data DAS used, their literature source, and how the calculations were performed are presented in Appendix E. Total MOEs were calculated for single uses by aggregating the dermal, oral, and inhalation exposures. Finally, probabilistic techniques, such as Monte Carlo, should be considered to further refine assessments which do not pass the Tier II assessments.

d. DAS Assessments Using Rex

Broadcast spray turf applications using Dursban Pro specialty insecticide and Dursban 50W Insecticide were assessed at the maximum use rate of 4 lb/acre and the typical use rate of 1 lb/acre. The algorithms used to derive exposures along with the input values used are described in Appendix E. In order to calculate the typical 1 lb/acre use rate, the data collected for the 4 lb/acre use rate was divided by a factor of four, assuming the data was linear in nature. The results of these calculations are shown in Table 1 for children and Table 2 for adults. Exposures were typically less than that reported in the EPA HED document. Dursban 50W turf applications

at a use rate of 4 lb/acre was the only use which for children had a total MOE lower than 10 (MOE = 8). However, further refinement of this Tier II assessment by using Monte Carlo probabilistic techniques to determine the distribution of dislodgeable data resulted in MOE for children of the 97.5 percentile. All other turf uses exceeded a total MOE of 10, which is acceptable, based on human toxicological data. Many of the total MOEs for a single use were in the 100 plus range. Additionally, comparisons were made between the maximum application rate and the typical application rate for a given use. As would be expected, the resulting exposures are significantly lower and should be considered since this represents greater than 50% of the use pattern. Total MOEs for Dursban 50W at 1 lb/acre and Dursban Pro at 1 and 4 lb/acre exceed the required MOE of 10, indicating a high degree of safety for these products when used individually.

Granular turf applications were assessed at the maximum use rate of 2 lb/acre and the typical use rate of 1 lb/acre. The algorithms used to derive exposures along with the input values used are described in Appendix E. In order to calculate the typical 1 lb/acre use rate, the data collected for the 2 lb/acre use rate was divided by a factor of two, assuming the data was linear in nature. The results of these calculations are shown in Table 1 for children and Table 2 for adults. Exposures were typically lower than that reported by the EPA HED document. MOEs were greater than 1000 for all exposures and in many cases they were greater than 10,000. Thus, the MOEs easily exceed the required MOE of 10, indicating a high degree of safety for this product.

Crack and crevice applications were assessed at the maximum use rate of 0.5% chlorpyrifos in dilute solution and the typical use rate of 0.25%. The algorithms used to derive exposures along with the input values used, are described in Appendix E. In order to calculate the typical 0.25% dilute solution use rate the data collected for the 0.5% dilute solution use rate was divided by a factor of two, assuming the data was linear in nature. The results of these calculations are shown in Table 1 for children and Table 2 for adults. Exposures were lower than that reported by the EPA in a majority of cases. MOEs were greater than 100 for all exposures and in many cases they were greater than 1000. Thus, the MOEs easily exceed the required MOE of 10 (using human data), indicating a high degree of safety for this product.

A single termiticide scenario, seven days after treatment to a home with a basement, was assessed at a 1% use rate. The algorithms used to derive exposures along with the input values used, are described in Appendix E. The results of these calculations are shown in Table 1 for children and Table 2 for adults. While exposures were higher than that reported by the EPA, the MOE was greater than 100 for inhalation exposures. Thus, the MOE for this termiticide scenario exceeds the required MOE of 10 (based on human data), indicating a high degree of safety for this product.

Simple aggregation of exposure from the use of granular turf, crack and crevice, and termiticide using typical application rates results in aggregated MOE of 161 and 578 for children and adults, respectively. These values still exceed the acceptable MOE of 10 by a factor of 10 or greater. Furthermore, it is highly unlikely that a single individual would be exposed via turf (granular), termiticide, and crack and crevice uses at the same time. A detailed study of chlorpyrifos use aggregation was conducted by Francis and Shurdut (Francis, 1996)and provided to EPA.

In conclusion, DAS Rex-based assessments for the four use examples exceeded the acceptable MOE of 10 based on human toxicological data with the exception of exposure to children with Dursban 50W Insecticide at 4 lb/acre. However, further refinement of the Dursban 50W 4lb/acre Tier II assessment by using Monte Carlo probabilistic techniques resulted in MOE for children of 15 at the 97.5 percentile. Many of the total MOEs for a single use were in the 1000 plus range. Additionally, comparisons were made between the maximum application rate and the typical application rate for a given use. As would be expected, the resulting exposures are significantly lower and should be considered since this represents a significant portion of the use pattern. For example, use of the typical liquid spray turf application rates compared to the maximum rates resulted in the total MOE being raised by a factor of four for both children and adults. The DAS risk assessment indicates a high degree of safety for chlorpyrifos use in residential setting provided the label is followed. As shown with the 4 lb Dursban 50W use on turf, further refinement of these exposure assessments using Monte Carlo probabilistic techniques results in

even lower exposures. Further refinement of these exposure assessments using Monte Carlo probabilistic techniques would likely result in even lower exposures.

Table 1. Post-Application Residential Exposures and MOEs for Children

Reentry Scenario	Dose (ug/kg/day)		MOE (Acceptable in bold)	
	EPA HED	DAS	EPA HED	DAS
Turf Application at 4 lb per acre with Dursban 50W (short term exposure)				
Inhalation	NR	1.41	NR	**354**
Dermal	NR	28.47	NR	**18**
Oral	NR	29.41	NR	**17**
Total	*NR*	59.29	*NR*	8***(15)***[b]
Turf Application at 1 lb per acre with Dursban 50W (short term exposure)				
Inhalation	NR	0.35	NR	**1415**
Dermal	NR	7.12	NR	**70**
Oral	NR	7.35	NR	**68**
Total	*NR*	14.82	*NR*	*34*
Turf Application at 4 lb per acre with Dursban Pro (short term exposure)				
Inhalation	5	1.41	20	**354**
Dermal	414 (12.42) [a]	6.47	12	**77**
Oral	1.26	6.80	**400**	**73**
Total	*18.68*	*14.68*	*7.5*	***34***
Turf Application at typical 1 lb per acre use rate with Dursban Pro (short term exposure)				
Inhalation	NR	0.35	NR	**1414**
Dermal	NR	1.62	NR	**309**
Oral	NR	1.70	NR	**294**
Total	*NR*	*3.67*	*NR*	***136***
Turf Application at 2 lb per acre with Dursban 2.5G (short term exposure)				
Inhalation	0.25	0.07	**400**	**6843**
Dermal	56 (1.68) [a]	0.13	90	**3864**
Oral	0.085	0.21	**6000**	**2414**
Total	*2*	*0.41*	*73*	***1221***
Turf Application at typical 1 lb per acre with Dursban 2.5G (short term exposure)				
Inhalation	NR	0.04	NR	**13686**
Dermal	NR	.07	NR	**7729**
Oral	NR	.10	NR	**4828**
Total	*NR*	*0.21*	*NR*	***2442***
Crack & Crevice (0.5%) (short term exposure)				
Inhalation	0.18	1.43	130	**350**
Dermal (carpets)	53.4 (1.60) [a]	0.50 (total)	94	**1009**
Dermal (surfaces)	26.7 (0.80) [a]		187	
Oral	1.67	0.51	299	**981**
Total	*NR*	*2.43*	*NR*	***205***
Crack & Crevice (0.25%) (short term exposure)				
Inhalation	NR	0.72	NR	**700**
Dermal (carpets)	NR	0.25 (total)	NR	**2018**
Dermal (surfaces)	NR		NR	
Oral	**NE**	0.26	**NE**	**1963**

Total	*NR*	*1.22*	*NR*	***411***
Termiticide (short term exposure)				
Inhalation (Day 7; Basement)	*0.37*	*1.68*	*270*	***297***

NE = No Exposure NR = Not Reported NC = Not Calculated

[a]Values in parenthesis for EPA-HED exposure reflect adjustment for 3% dermal adsorption.

[b] Using Monte Carlo simulations for exposure calculations at the 97.5 percentile.

Table 2. Post-Application Residential Exposures and MOEs for Adults

Reentry Scenario	Dose (ug/kg/day)		MOE (Acceptable in bold)	
	EPA HED	DAS	EPA HED	DAS
Turf Application at 4 lb per acre with Dursban 50W (short term exposure)				
Inhalation	NR	0.23	NR	**41**
Dermal	NR	12.23	NR	**2186**
Oral	**NE**	NE	**NE**	**NE**
Total	*NR*	12.46	*NR*	**40(*71*)[c]**
Turf Application at 1 lb per acre with Dursban 50W (short term exposure)				
Inhalation	NR	0.06	NR	**8744**
Dermal	NR	3.06	NR	**164**
Oral	**NE**	NE	**NE**	**NE**
Total	*NR*	3.12	*NR*	**161**
Turf Application at 4 lb per acre with Dursban Pro (short term exposure)				
Inhalation	0.59	0.23	170	**2186**
Dermal	510 (15.3) [a]	2.78	10	**180**
Oral	NE	NE	NE	**NE**
Total	*6.3*	*3.01 (0.34) [b]*	*9*	***166***
Turf Application at 1 lb per acre with Dursban Pro (short term exposure)				
Inhalation	NR	0.06	NR	**8744**
Dermal	NR	0.70	NR	**720**
Oral	NE	NE	NE	**NE**
Total	*NR*	*0.76*	*NR*	***665***
Turf Application at 2 lb per acre with Dursban 2.5G (short term exposure)				
Inhalation	0.3	0.01	**330**	**42278**
Dermal	27 (0.81) [a]	0.06	190	**8997**
Oral	NE	NE	NE	NE
Total	*1.4*	*0.07 (2.48) [b]*	*120*	***7418***
Turf Application at 1 lb per acre with Dursban 2.5G (short term exposure)				
Inhalation	NR	0.01	NR	**84555**
Dermal	NR	0.03	NR	**17994**
Oral	NE	NE	NE	**NE**
Total	NR	0.04	NR	**14836**
Crack & Crevice (0.5%) (short term exposure)				
Inhalation[b]	0.18	0.43	**560**	**1158**
Dermal (carpets)	56.5 (1.70) [a]	0.21 (total)	88	**2349**
Dermal (surfaces)	28.2 (0.85) [a]		177	
Oral	NE	NE	NE	**NE**
Total[g]	*NR*	*0.65 (0.16) [b]*	*NR*	***775***
Crack & Crevice (0.25%) (short term exposure)				
Inhalation	NR	0.22	NR	**2315**
Dermal (carpets)	NR	0.11 (total)	NR	**4698**
Dermal (surfaces)	NR		NR	

Oral	**NE**	NE	**NE**	**NE**
Total	*NR*		*NR*	***1551***
Termiticide (short term exposure)				
Inhalation (Day 7; Basement)	*0.11*	*0.51*	***910***	***983***

NE = No Exposure NR = Not Reported NC = Not Calculated
[a]Values in parenthesis for EPA-HED exposure reflect adjustment for 3% dermal adsorption.
[b] Highest biomonitoring values derived from Vaccaro et al., 1993; Vaccaro et al., 1996; Byrne et al., 1998.
[c] Using Monte Carlo simulations for exposure calculations at the 97.5 percentile.

E. Incident Review

- Poison Center "methodology" as referred to in the reference "Blondell (1999)" misrepresents poison center practice and how that practice impacts the quality, substance, and detail of Toxic Exposure Surveillance System (TESS)-derived data, which is extensively relied upon as the basis for the conclusions presented in this section. See Appendix G for specific comments to this document.
- Although it is implied that the Incident Data System Reports mandated by, and reported through, the EPA 6(a)(2) process are utilized in the section analysis, it appears this data are specifically excluded from the analysis.
- The case for "Chronic Effects" is heavily weighted with single "Case Reports" that are anecdotal, unsubstantiated accounts of exposure, none of which have been corroborated through independent physician assessment with documented laboratory confirmation of exposure.
- There are a number of instances where numbers and corresponding percentages are inconsistent with published TESS data.
- Statements presented as fact are not supported by the data presented.
- There are inappropriate extrapolations related to incident rates and anticipated exposure estimates that are not, and cannot, be supported by the available data.
- The "five measures" outlined to determine one's risk from chlorpyrifos exposures are inexact, inappropriate, and subject to miscalculation for the stated purpose.
- Reference to "chronic neurobehavioral effects and multiple chemical sensitivity" engenders the belief that 1) there is an unqualified existence of such effects and/or syndrome; 2) a recognized

cause and effect relationship between chlorpyrifos and such effects exists; and, 3) the data presented in this document are capable of demonstrating an association or cause and effect relationship between these effects and chlorpyrifos. Each of these beliefs both singly and in relation to each other are scientifically and medically unfounded, unsubstantiated, and unwarranted.

- In the absence of scientific, peer reviewed, or published studies documenting or confirming allegations of human toxicity from exposure incidents involving chlorpyrifos, the Agency has chosen to rely in large part on a computerized dataset of poison center data from a database which:

  -- is totally dependent on voluntary reporting
  -- involves passive collection of incident information and contains no "prospective" component of substance or category-specific data collection
  -- has no means to confirm or corroborate reported incidents
  -- is largely comprised of consumer self-reported symptoms made by telephone (87%)
  -- does not permit researchers access to "original" case records and notes for purposes of verifying or qualifying case details
  -- has been the subject of quality issues with as many as 38% of reported outcomes being coded inaccurately as determined by audits sponsored by the trade organization that sells the data
  -- contains anonymously reported information
  -- cannot sustain the necessary scientific rigor to support the conclusion drawn from it because it contains no data fields to document exposure circumstances, dose, confirmatory laboratory findings, differential diagnosis, and, in 30% of the organophosphate reported incidents, which agent or active ingredient is actually involved

It is hard to imagine a more convincing set of facts for a finding of arbitrary and capricious decision making by the Agency. In fact, the bases for the Agency's conclusions, the incident

reviews known as the "Blondell Reports," have recently been found to lack any foundation in science or medicine by a court of law.

On February 4, 1998, the District Court for the Sixth Judicial District, St. Louis County (Duluth), Minnesota, entered summary judgment in favor of The Dow Chemical Company and Dow AgroSciences in litigation arising from a residential application of Dursban insecticide. That decision has now been affirmed by The Minnesota Court of Appeals. In ordering summary judgment, the trial court excluded from evidence the January 1995 memorandum entitled "*Review of Chlorpyrifos-Associated Cases of Delayed Neuropathy,*" authored by Jerome Blondell, Ph.D., and the January 1997 memorandum entitled "*Review of Chlorpyrifos Poisoning Data,*" prepared by Jerome Blondell, Ph.D. and Virginia Dobozy, V.M.D., M.P.H.

The Court found the "Blondell memoranda" to be scientifically unreliable and therefore inadmissible in evidence. In so holding, the Court stated the following:

> Order Excluding Blondell Memoranda, Conclusions of Law:
>
> #1 "The Blondell Memoranda, consisting of anecdotal information gathered pursuant to a methodology not generally accepted in either the scientific or medical communities as a mechanism to establish a cause and effect relationship between chemical exposure and neurological health problems, lack sufficient probative value to render it appropriate for submission to the [jury]."
>
> #2 "Failing to employ a methodology accepted by even a significant minority of the relevant scientific or medical communities, the Blondell Memoranda are not sufficiently reliable and probative to make them appropriate for consideration by the [jury]."
>
> Memorandum in Support of Order Excluding Blondell Memoranda:
>
> "[T]he Blondell Memoranda constitute hearsay and some of the memoranda's contents might be characterized as third-hand hearsay. Unknown persons made telephonic report to unknown persons who made some sort of notations regarding the reports according to a protocol which has not been shown to have been consistent among the call takers." (p 1)

> "Likewise, there has been a total failure to specifically address dose/response methodology in the Blondell work." (p 3)
>
> "As pointed out by the defendants, there is no showing that the authors of the Blondell Memoranda are possessed of sufficient scientific knowledge and experience to justify any attempt by them to draw a causative link between chemical exposure and neurologic deficits constituting neurological abnormalities." (pp 3-4)

1. Comments Pertaining to the Chlorpyrifos Incident Review Update Dated June 30, 1999

Page 2, summary: *"In addition to acute poisoning, chlorpyrifos has been reported to be associated with chronic effects in humans, including chronic neurobehavioral effects and multiple chemical sensitivity. Neurobehavioral effects reported include persistent headaches, blurred vision, unusual fatigue or muscle weakness, and problems with mental function including memory, concentration, depression, and irritability. Such effects have been reported in a small proportion of the acute symptomatic cases…*

The "chronic neurobehavioral effects" reported to be associated with chlorpyrifos exposure are non-specific and, in general, subjective complaints which are difficult if not impossible to verify objectively. As will be discussed in further detail below, these symptoms have been commonly evoked as evidence of "environmental illness" since before the time organophosphate pesticides began to be manufactured. The so-called MCS is a symptom complex dismissed as unproven and lacking scientific basis by most of the scientific medical community, as well as a significant number of jurists. Among those professional associations rejecting MCS as a legitimate medical diagnosis are The American Medical Association Council on Scientific Affairs, the American Academy of Allergy, Asthma and Immunology, the American College of Occupational and Environmental Medicine, the World Health Organization, the Agency for Toxic Substances and Disease Registry of the Department of Health and Human Services, the American College of Physicians, the International Society of Regulatory Toxicology and Pharmacology, and the California Medical Association. While all claims of potential chemically-related illness should be recorded and studied prospectively when warranted by significant incidence, the inclusion of such unsubstantiated allegations has no place in an EPA regulatory evaluation.

Page 2, AAPCC database. "*PCCs are staffed by Poison Information Specialists who are available 24 hours a day, 365 days a year to provide poison information, telephone management and consultation, and collect pertinent data on each exposure.*"

The term "Poison Information Specialist" was coined in recognition of the fact that the training and expertise of those responding to calls varies considerably both within and between centers. The referenced document (Blondell 1999) leaves the impression these specialists are uniformly certified by the American Association of Poison Control Center (AAPCC). This, in fact, is inaccurate. Poison center (PC) calls are responded to not only by licensed professionals such as clinical pharmacists and registered nurses, but also by uncertified, unlicensed "specialists." The training required is determined by each center. While a CSPI must be on duty 24 hours, non-certified personnel can and do respond to calls. These uncertified personnel often serve an important role in triage and in management of general information and non-exposure calls. Their ability to determine likelihood of association of reported symptoms to a reported exposure, however, is directly related to their training and experience in clinical toxicology. It should be pointed out that very few poison information specialists, including CSPIs, have significant training in industrial hygiene, which is clearly important in the evaluation of "environmental" exposures.

The majority of calls come from the lay public, some of whom may call when exposure is assumed but not confirmed (e.g., infant next to an open container). Lay persons may report symptoms less accurately which must be translated into specific medical terminology by Poison Information Specialists."

While correct, this statement underestimates the logistical difficulties encountered in determining plausibility of association of a reported "exposure" with a symptom or symptoms. For example, it is not unusual to receive calls from a person who has "used a pesticide product" days to weeks (or months) before the onset of "typical" symptoms of organophosphate toxicity, such as nausea, headache, or diarrhea. The non-specificity of such signs, in concert with the uncertainty of any documented exposure (spill, splash, ingestion), renders the determination of association almost completely subjective, even for the seasoned poison information specialist.

Page 3, first full paragraph. "*Of the 116,225 unintentional pesticide exposures to single products in 1996, 19,033 or 16% were due to organophosphate pesticides, and 5,188 or 4.5% were due to chlorpyrifos (AAPCC 1998).*"

The figures above are not consistent with those found in the summary data of the 1996 AAPCC Annual Report (Litovitz et al., 1996). Table 22A lists 15,973 exposures to organophosphates only, with 15,197 unintentional exposures. The number due to chlorpyrifos is not indicated in summary data. Thus, if the figure of 19,033 is 25% higher than the corresponding number that is published in the annual report, the accuracy of the 5,188 figure and all subsequent calculations and reported percentages is in question.

"*Given that 30% of organophosphates were not specifically identified by active ingredient, the actual number of chlorpyrifos cases reported to AAPCC is probably close to 7,000, or 6% of all the pesticide-related exposures.*"

Extrapolation of these figures is speculative. It is impossible to know whether the percentage of chlorpyrifos among unidentified organophosphates is similar to the proportion of identified organophosphates. More importantly, the fact that 30% of "organophosphates" are unidentified in this dataset raises significant questions regarding its utility. How can it be that the most important single element in a toxicology-related call, that is, specific identification of the toxin in question, is missing in one-third of cases? How does one identify a compound as an "organophosphate" without knowing the active ingredient? It seems highly unlikely the caller (>80% laypersons) is educated enough about a product to identify it for the poison information specialist as an "organophosphate" if he/she cannot find the list of active ingredients on the label. Who then, determines that the product in question is an organophosphate, and on what basis?

"*Many of these exposures involve small children who are exposed but never develop symptoms. Increased use of child-resistant packaging would markedly reduce these exposures.*"

While few would argue that child-resistant packaging helps to reduce the incidence of unintentional exposures in children, the source of the data supporting this statement is unclear. AAPCC data do not routinely identify problems with packaging or presence or absence of child-

resistant devices. How many of these exposures involve products without child-resistant packaging? How many of these products without child-resistant packaging are approved for home use? And, most importantly, in how many of these cases was the product out of the original container, such as the case of the one fatality where the product was outside of its original packaging in a beverage cup?

"*Of the cases receiving followup, a minority experienced moderate effects (7.7%), major or life-threatening effects (0.4%), and there was one fatality. The other 92% either developed no symptoms or minor symptoms as a result of their exposure.*"

It is apparent that when reporting case "percentages" with particular types of medical outcomes, these percentages are based on cases with what is termed "known outcomes." It should be noted the categories of "not followed; nontoxic" and "not followed: minimal toxicity" are not considered in these numbers despite the fact that the poison information specialist is making an assessment that the exposure is of a trivial nature requiring that no further patient contact is warranted. Excluding these categories exaggerates the significance of the percentages as does the exclusion of the various corresponding absolute numbers of cases on which some of the percentages are based (e.g., Tables 2 and 3).

In fact, if one looks at all exposures to organophosphates alone in 1996 (<u>including intentional suicide attempts</u>), only 568 of 15,973 (3.6%) had moderate effects, and 65 (0.46%) had major or life-threatening outcomes. As only 4% had moderate or major effects or death, 96% of all reported exposures resulted in no or minor reported symptoms.

Page 3, last paragraph. "*Five measures were selected by HED to assess the amount of hazard associated with chlorpyrifos relative to other insecticides, restricting the analysis to unintentional exposures in residential settings, involving a single product. These were: percent of all cases that were seen in a health care facility; percent of cases seen in a health care facility admitted to a hospital; percent of cases seen in a health care facility admitted to critical care; and of those cases receiving follow-up to determine outcome, percent with symptoms and percent with life-threatening symptoms.*"

These “measures to assess the amount of hazard” are inappropriate for a number of reasons.

1. The percentage of all cases that were seen in a health care facility.

    - This measure does not take into account the percentage of patients who decide on their own, in the absence of any advice by the poison information specialist or another health care provider, to be seen in a health care facility. The AAPCC emphasizes as the PC’s *raison d’être* that many visits to emergency departments and health care providers after reported exposures are unnecessary.

    - Poison information specialists are undoubtedly more likely to recommend evaluation by a health care facility after reported organophosphate exposure than many other insecticides, given the potential for toxicity by organophosphates as a class, relative to a group like the pyrethrins or boric acid, regardless of initial symptomatology.

    - Patients reporting unusual symptoms relative to any exposure scenario will typically be referred to their primary care provider by other poison information providers as a standard of practice regardless of whether the specialist believes the symptoms are potentially related to the incident. This is true in both calls made to public poison centers as well as calls made to the DAS product stewardship medical information system. To then suggest that this parameter is indicative of the “seriousness” of the event is unrealistic.

2. The percentage of cases seen in a health care facility admitted to a hospital.

    - Once again, given the known potential for toxicity of organophosphate in overdose, it is not uncommon for physicians to admit patients with *possible* exposure to organophosphates to the hospital for observation. Given that children are likely to vomit after chemical exposure (a sign of potential organophosphate toxicity), the likelihood of admission increases in this group.

    - There are also economic incentives to admit patients not under a capitation-type health plan to the hospital.

3. The percentage of cases seen in a health care facility admitted to critical care.

    - Certain hospitals have a standing policy that all patients with a diagnostic classification of “poisoning,” whether admitted for treatment or observation, be admitted to a critical care unit regardless of presence or absence of symptoms. The rationale for such policies is that nursing care is less intensive on the general medical floors, so sudden loss of consciousness or cardiorespiratory difficulties might go unnoticed, and because critical care nursing allows one-on-one supervision of potentially suicidal patients.

- Admission to a critical care unit is not necessarily indicative of gravity. Many physicians are uncomfortable managing poisoned patients due to their relative unfamiliarity with toxic effects and use of antidotes given the general lack of training in toxicology provided in medical training programs. Admission to the critical care unit increases the "comfort level" of the physician.

- Organophosphate-exposed patients are more likely to be admitted to critical care units because non-specific symptoms and signs (nausea and vomiting) may be perceived as early signs of organophosphate poisoning. Patients are thus admitted to the critical care unit in anticipation of the need for antidotes (atropine and pralidoxime). A much better index of the need for intensive care is the actual administration of antidotes in these patients which were found in a previous study to occur in less than 1% of all patients (Kingston et al.)

4. The percentage with symptoms and percentage with life-threatening symptoms.

    - General "symptoms," *per se*, may often have little to do with toxicity. The foul odor associated with many organophosphate products and/or their associated solvents, as well as the emotional response to belief that one has been poisoned, may lead to nausea, vomiting, headache, and many other non-specific symptoms in the absence of true toxicity. The *sine qua non* of organophosphate toxicity is generalized increased secretions, including salivation, tearing, sweating, and pulmonary secretions. Simple nausea and vomiting, while certainly of concern, cannot be attributed *stricto senso* to organophosphate poisoning.

    - The definition of life-threatening symptoms is utilized in the context of "major" outcome. In the absence of information indicating which patients required specific antidotes, endotracheal intubation and artificial ventilation, or circulatory support with vasopressors, these data are not meaningful indicators of hazard.

Finally, the direct comparison of organophosphates to other "insecticides" has little true meaning unless one compares products which have similar use patterns. To compare an efficacious termiticide like chlorpyrifos to a topical insect repellant intended for human application is meaningless. One cannot legitimately expect these two products to have similar toxicity! Rather, comparisons should be made between products destined for similar use.

Page 4, first full paragraph. "*The fatality was a 22 month old boy who accidentally ingested chlorpyrifos that had been placed in a cup.*"

There is no doubt chlorpyrifos contributed to the poisoning of this child, based on the depression of plasma cholinesterease reported in the AAPCC report (Litovitz et al., 1996). However, the report makes it very clear that aspiration of petroleum distillates was important to the outcome, as evidenced by immediate choking. His death was due, not to acute cholinergic crisis, but to sepsis secondary to respiratory failure, a well-documented complication of petroleum distillate aspiration. This should be made clear in the evaluation.

EPA's report also mentions that chlorpyrifos has been associated with multiple chemical sensitivities whose symptoms often include, interestingly enough, many of the "neurobehavioral effects" cited above. EPA's report fails to mention the vast majority of the medical community and a significant proportion of the nation's judges have determined there is insignificant scientific evidence to support the existence of "multiple chemical sensitivities."

The American Medical Association (AMA) has stated:

> "*Two medical societies have issued position papers and one has issued an informational report on clinical ecology [N.B. the "specialty group" espousing multiple chemical sensitivities]. The position papers reported that no scientific evidence supports the contention that MCSS is a significant cause of disease or that the diagnostic tests and the treatments used have any therapeutic value. Until such accurate, reproducible, and well-controlled studies are available, the American Medical Association Council on Scientific Affairs believes that multiple chemical sensitivity should not be considered a recognized clinical syndrome.*" (AMA, 1992)

The American Academy of Allergy, Asthma and Immunology (AAAAI) has also commented on clinical ecology:

> "*Clinical ecology is an approach to medicine that ascribes a wide range of symptoms to exposure to numerous common substances in the environment. Advocates of this practice describe themselves as "ecologically oriented." Patients are said to be "environmentally ill," or "hypersensitive" or "allergic" to environmental factors such as food, water, chemicals, and pollutants…An objective evaluation of the diagnostic and therapeutic principles used to support*

> *the concept of clinical ecology indicates that it is an unproven and experimental methodology…Advocates of this dogma should provide adequate clinical and immunologic studies supporting their concepts, which meet the usually accepted standards for scientific investigation.*" (American Academy of Allergy, Asthma and Immunology, 1986)

Also, in 1999, the AAAAI issued a second position statement. That statement adopted a new name recommended by a World Health Organization workshop: Idiopathic Environmental Intolerance. The statement also concluded:

- Because of the varied and subjective nature of the illness, no precise case definitions or diagnostic criteria exist.
- The list of environmental chemical exposures triggering symptoms is virtually unlimited.
- There have been no dose-response studies of this phenomenon, but patients report that these materials provoke symptoms at concentrations at or below commonly encountered ambient levels. Furthermore, symptoms bear no relationship to established toxic effects of the specific chemical and occur at concentrations far below those expected to elicit toxicity.
- There are no diagnostic symptoms, and there are no diagnostic objective physical signs. Many different tests and procedures have been proposed, but no single test or combination of tests has been validated as diagnostic . . . . Studies to date have failed to confirm that any immunologic tests are diagnostic for chemically-induced symptomatology.
- Rigorously controlled studies to verify that patients reported subjective sensitivity to specific environmental chemicals have yet to be done.
- Moreover, there is no evidence that these patients have any immunologic or neurologic abnormalities.

Recently, the American College of Occupational and Environmental Medicine (ACOEM) has reiterated their position on MCS:

> "*Since the publication of earlier position statements by the American College of Occupational and Environmental Medicine (ACOEM), the diagnosis, treatment and etiologic assessment of multiple chemical sensitivities (MCS) has remained a troublesome medical and social concern for individuals, physicians, government and organizations. First described in 1952, the syndrome has since engendered more than 20 names, including "environmental illness," "total allergy* th *century disease," and "chemical AIDS." These terms refer to*

> *complaints of patients who report recurrent non-specific symptoms referable to multiple organ systems that the sufferers believe are provoked by exposure to low levels of chemical, biological, or physical agents. No consistent physical findings or laboratory abnormalities have yet been found to differentiate MCS patients from the remainder of the population…ACOEM concurs with many prominent medical organizations that evidence does not yet exist to define MCS as a distinct entity…ACOEM continues to support the position that the relationship of MCS to environmental contaminants remains unproven. No scientific basis currently exists for investigating, regulating, or managing the environment with the goal of minimizing the incidence or severity of MCS."* (ACOEM, 1999)

The overwhelming majority of state and federal courts across the country have excluded or criticized opinion testimony regarding MCS because it is unreliable and not generally accepted among the medical or scientific communities. In *Frank v. State of New York*, 972 F. Supp. 130 (N.D.N.Y. 1997), a case involving an alleged exposure to Dursban, the Court conducted a detailed analysis of the case law and literature and concluded that expert opinions relating to MCS should be excluded since they fail to satisfy any of the admissibility factors adopted by the U.S. Supreme Court in *Daubert v. Merrell Dow Pharmaceuticals, Inc.* 509 U.S. 589 (1993). With regard to the *Daubert* factor of "testability," the court noted that "[i]n the view of one commentator, the lack of valid, objective testing procedures for MCSA is one of its defining features…The lack of objective physical signs of abnormality or pathology in MCS sufferers is confirmed by both the American College of Physicians and the American Academy of Allergy and Immunology." *Id*. at 133. The Court further stated that "[t]o the extent that the MCS theory has been tested, such tests failed to provide objective support for the notion that the symptoms complained of by MCS sufferers are caused by environmental pollutants." *Id.* at 133-34. With respect to the rate of error factor, the Court stated: "Finally, as defendants point out, the lack of an objective testing method for MCS gives rise to high probability of error in MCS diagnoses." *Id.* at 135.

The Court also noted that "[p]eer review of the MCS theory has revealed a host of flaws in the theory, warranting skepticism as to the validity of MCS." *Id*. at 135. On the "general

acceptance" of MCS, the Court stated: "Moreover, MCS' status in the medical community is a far cry from general acceptance….MCS also has failed to gain acceptance in the field of toxicology." *Id.* at 135-36. In sum, the Court concluded:

> *Every federal court that has addressed the issue of the admissibility of expert testimony on MCS under Daubert has found such testimony too speculative to meet the requirement of "scientific knowledge."… This court is compelled to reach the same conclusion in the present case.* The materials submitted by defendants establish that the theory underlying MCS is untested, speculative, and far from general acceptance in the medical or toxicological community.

Id. at 136-37 (emphasis added).

In *Coffin v. Orkin Exterminating Co. Inc.*, 20 F. Supp. 2d 107 (Me. 1998), plaintiff's expert alleged that the plaintiff contracted MCS as a result of exposure to pesticides. The Court reviewed the extensive line of authority unanimously excluding testimony relating to MCS and "adopted the reasoning and conclusions" of the Court in *Frank* and excluded the plaintiff's expert testimony. *Id.* at 111.

Other federal and state courts have also excluded or criticized opinion testimony relating to MCS. *See Coffey v. The County Home of Hennepin*, 23 F. Supp. 1081, 1086 (D. Minn. 1998) (court "failed to find an article or a medical association which opines that the methodology of diagnosing MCS has progressed to a point that it is scientific knowledge capable of assisting a fact-finder."); *Treadwell v. Dow-United Technologies*, 970 F. Supp. 974, 982 (N.D. Ala. 1997) ("[T]he Court finds inadmissible any evidence offered by [plaintiffs' expert] propounding a diagnosis of multiple chemical sensitivity, as well as any causes and treatments grounded in the etiology of MCS and clinical ecology"); *Sanderson v. International Flavors and Fragrances, Inc.*, 950 F. Supp. 981, 1002 (C.D. Cal. 1996) ("[T]he Court has discovered no case in which MCS was recognized as a legitimate medical condition."); *Cavallo v. Star Enterprise*, 892 F. Supp. 756, 768 (E.D. Va. 1995) (court refused to admit the plaintiff's expert testimony on causation noting that the studies supporting the expert's opinions of MCS were unreliable because of the "questionable scientific

validity of MCS."); *Zwillinger v. Garfield Slope Housing Corp.*, 1998 U.S. Dist. LEXIS 21107, *61-62 (E.D. N.Y. August 17, 1998) ("every federal court that has considered the admissibility of expert testimony concerning multiple chemical sensitivity has found the basis for the diagnosis to be too speculative to qualify as 'scientific knowledge' under *Daubert.*"); *Carlin v. RFE Industries*, 1995 WL 760739, *6 (N.D.N.Y. November 27, 1995) ("The Court…concludes that plaintiffs' exhibits do not establish that the evidence of multiple chemical sensitivity is currently known or tested."); *Underwager v. Salter*, 22 F. 3d 730, 736 (7th Cir.) (finding that the controversy surrounding MCS remained to be "settled by the methods of science rather than by the methods of litigation"), *cert. denied*, 513 U.S. 943 (1994); *La-Z-Boy Chair Co. v. Reed*, 936 F.2D 573 (table), 1991 U.S. App. LEXIS 14137, *1-2 (6th Cir. June 28, 1991) (affirming district court's refusal to rely on clinical ecologist's testimony regarding MCS). *See also Donato v. Metropolitan Life Ins. Co.*, 19 F.3d 375, 380 (7th Cir. 1994) (affirming denial of disability benefits); *Brown v. Shalala*, 38 F.3d 232 (5th Cir. 1994) (holding that "'ecological illness' is not accepted widely, and no 'yes or no' test apparently exists…."), *cert. denied*. 514 U.S. 1120 (1995); *Kouril v. Bowen*, 912 F.2d 971 (8th Cir. 1990) (same); *Lawson v. Sullivan*, 1990 U.S. Dist. LEXIS 18758 (N.D. Ill. Oct. 30, 1990) (magistrate report), adopted in 1991 U.S. Dist. LEXIS 1560 (N.D. Ill. Feb. 6, 1991) (same); S*mith v. Chesapeake & Potomac Tel. Co*, 1995 Va. App. LEXIS 381 (Va. Ct. App. Apr. 18, 1995) (affirming denial of workers' compensation benefits for alleged MCS); *Chanin v. Eastern Va. Med. Sch.*, 459 S.E.2d 523 (Va. Ct. App. 1995) (same); *Ruether v. Minnesota*, 455 N.W.2d 475 (Minn. 1990) (same).

EPA is perhaps aware of the judge's decision in Bahura et al. v. S.E.W. Investors et al. (No. 90-CA-10594, District of Columbia Superior Court, November 29, 1995), a "sick building syndrome" action brought by EPA workers claiming MCS toxic encephalopathy caused by building renovations. The judge rejected Dr. Iris Bell's testimony on "limbic kindling" as unreliable and not generally accepted in the fields of neurology or psychiatry, and that low-level exposure to everyday chemicals does not cause permanent injury.

In Carroll v. Marion County Board of Education (No. 92-C-196, WV Circuit, Marion Co. Div. 1), the judge refused to allow Dr. Grace Ziem to testify that the plaintiff's son suffered MCS after alleged long-term exposure to pesticides at the school. The judge noted that MCS did not pass the "good science test," that the diagnosis of MCS has been almost universally rejected by the medical and scientific community, and the methodology supporting MCS was "somewhat

There are numerous other examples of the testimony of clinical ecologists being excluded from the courtroom on the basis of the lack of scientific evidence of multiple chemical sensitivities (Staudenmeyer, 1999; Barrett et al., 1998).

Page 6, Table 1. Number of exposures, symptomatic cases…

The number of life-threatening cases reported in this table does not correspond with the information given on page 4. This table suggests 19 life-threatening effects as compared to 35 listed on page 4. When calculating the percentage of life threatening illness overall the number is 0.14% and for PCO/Child, it is 0.08%, significantly smaller than the 0.456% reported previously.

Page 6, Table 2. PCO compared with non-PCO use…

It is not clear from this table how many of the exposures were occupational in origin. It is clear that PCOs often use products of greater concentration than those found normally in the home; thus, it is not surprising that a larger portion of reported exposures would result in hospitalization or significant symptoms. However, the inclusion of occupational exposures to the PCO personnel, potentially resulting from failure to follow recommendations for PPE or preparation guidelines, has little bearing on the issue at hand, i.e., the safety for the general public of household applied pesticide products.

Page 7, second paragraph. "*Prospective follow-up of the cases reporting symptoms to Poison Control Centers is needed to determine their persistence, incidence, and severity of chronic complaints.*"

This statement is interesting when placed in context of EPA's summary dismissal of the validity of Incident Data System Reports (p 9). In fact, during the last three years, longitudinal data documenting the duration of symptoms in patients reporting adverse effects of chlorpyrifos exposure have been collected and transmitted to the EPA through the Incident Data System. It seems odd that if over 3000 new reports alleging adverse health effects have been reported since June 1992 that there was "insufficient documentation confirming exposure or health effects to warrant a detailed analysis of these reports." One wonders then what the purpose of the FIFRA 6(a)(2) reports might be. Furthermore, DAS has proactively implemented a comprehensive product stewardship surveillance program through two independent PCs with professional staff from the University of Minnesota. Yet, data collected through this program have been virtually ignored in this report citing "insufficient documentation" confirming exposure or health effects to warrant a detailed analysis. It is curious that the PC incident data collected through this program is more comprehensive, more detailed, and subjected to higher standards of quality control and review than any of the data reported to TESS. A major part of this program includes the collection of laboratory specimens, at DAS expense, to perform cholinesterase testing. It should also be emphasized that "full text and notes" are available for review as opposed to TESS data, in which case details and notes are withheld and unavailable for review. It seems incredulous that TESS data would be subjected to such intense analysis yet this other data summarily dismissed.

Page 9, Incident Data System Reports. Referring to FIFRA 6(a)(2) incident data, EPA commented, "There was insufficient documentation confirming exposure or health effects to warrant a detailed analysis of these reports."

The EPA review appears to focus on 10 data elements collected through the TESS system. Despite comments from EPA suggesting that FIFRA 6(a)(2) incident data is not detailed enough to draw any conclusions, we find quite the contrary. Note the comparison of TESS data fields

utilized in the EPA review as compared to the FIFRA 6(a)(2) data submitted by DAS and potentially by other registrants.

Comparison of DAS DAS FIFRA 6(a)(2) with Chlorpyrifos Data Utilized by EPA

TESS DATA	DAS FIFRA 6(a)(2) Incident Data
Total number of cases	All incidents involving any alleged exposure with subsequent adverse effects is reported to the Agency regardless of relatedness. FIFRA 6(a)(2) guidelines do not require reporting of exposures resulting in no adverse effects, although DAS has provided this data as a courtesy to the Agency in an effort to share surveillance information. The Agency has the necessary raw data to compare like sets of data which includes both "potentially related" and unrelated cases as assessed by independent toxicology experts in the field.
Outcome severity	Each case in the DAS surveillance system is assessed for severity according to FIFRA 6(a)(2) criteria which is based, in large part, on AAPCC outcome criteria. In addition, all narative associated with the case is also provided as supporting documentation.
Relatedness of symptoms to the outcome severity	Each symptom in each DAS incident case is assessed for potential relatedness to the product involved using criteria similar to that used by the EPA in some of its state pesticide surveillance programs (e.g., "consistent," "inconsistent" and "unknown consistency (indeterminable)." This is an independent assessment done by poison center toxicology experts that are intimately familiar with the TESS process and includes three levels of Q/A. This process is believed to be more rigorous than that provided by most, if not all, public poison centers participating in TESS and includes narrative justification for the assessments that are provided where appropriate.
Product Identification: Product	Product identification in the DAS FIFRA

identification is almost uniformly accomplished using the MicroMedix Poisindex system which matches the name given by the caller to one product in the product list. If there is a mistake in identifying the exact product from the list, all subsequent codes assigned to that product identification will also be in error.	6(a)(2) incident reports include identification using five independent variables. These product identification variables are requested from the caller for each product involved and help determine the overall level of integrity of product identification. They include: 1) product name; 2) active ingredient; 3) UPC code, where available; 4) EPA registration number; and, 5) lot number. The more information collected to identify the product in question the better the match and assurance that the product has been appropriately identified.
Patient flow (e.g., hospital/medical care and hospital admission information)	Each case record provides detail of patient management flow, both in narrative and specific coding, consistent with TESS formating.
Signs and symptoms	Each reported sign and symptom is recorded for each incident as is done in the TESS system. Each sign and symptom is also coded for "relatedness" or "consistency" based on available information and level of detail provided by the caller. This is similar to the TESS system, but because of the increased level of case detail and availability of confirming laboratory support, it might be argued that the final assessment benefits from better information being available.
Age	Age is included in each data set even to the detail of coding the patient's actual birth date as opposed to the open ended question of "how old is the patient" typically collected by poison centers participating in the TESS system. This compensates for previously inaccurate age identification in pediatric cases where a caregiver might refer to a child in the age range from 18-35 months as a "2 year" old.
Intentional vs unintentional exposure	Each case is coded as to the whether it is an "intentional" vs. "unintentional" act, the same as TESS. Since the case narrative is

	also included, the supporting documentation can help clarify any coding assessment.
Duration of symptoms	Each case includes this level of detail as compared to TESS.
Acuity of exposure	Each case is identified in terms of acuity (e.g., acute, chronic, acute on chronic), the same as the TESS data. In addition, the time from product exposure to onset of signs and symptoms is also included in this dataset. This is an extremely valuable element that is missing from TESS.

In the final analysis, the DAS FIFRA 6(a)(2) incident data provides all the same data fields relied upon by EPA for their assessment of TESS data, plus numerous additional data fields as required by EPA to the extent that that information is available from the caller. Any data unavailable in the DAS FIFRA 6(a)(2) incident data would most certainly be even less accessible or not collected in the TESS dataset.

Page 10, case reports. *"Dr. Wagner noted 'The most difficult problem has been encountered with chlorpyrifos. There have been 34 inquiries about this insecticide. The clinical problems most commonly raised have been complaints of long-term illness following acute exposure and/or intoxication.'"* (Wagner, 1990)

While published in the scientific literature, the report by Wagner is scarcely more than a rough tally of requests for information or consultation regarding illness potentially related to pesticides. In spite of the provocative statement above about chlorpyrifos, no other clinical information is provided about the cases, their specific complaints, any investigative studies done to confirm them (physical examination, laboratory studies), nor are there any bibliographic references provided.

A recent court decision demonstrates the inherent deficiencies in Dr. Wagner's case reports. In *Hannan v. Pest Control Services, Inc.,* Marion County, Indiana, Superior Court No. 49D02-9802-CT-173, (referred to by Dr. Wagner in his reports as EPA incident number 94-219), the

plaintiffs alleged various MCS-related symptoms resulting from an acute overexposure to chlorpyrifos and diazinon. The claims were rejected by the Court, which found:

(1) That the Plaintiffs' physicians had not utilized generally accepted toxicological methodology to establish a cause and effect relationship between the alleged exposure and the alleged illnesses, and had failed to follow scientific and medical methods practiced and generally accepted in their relevant fields;

(2) That the Plaintiffs' expert witnesses and treating physicians had failed to demonstrate under generally accepted toxicological methodology that chlorpyrifos or diazinon are capable of causing the health effects at issue;

(3) That the generally accepted diagnostic criteria (i.e., characteristic signs and symptoms) used to diagnose an acute over exposure to organophosphates were absent and not identified in these Plaintiffs; and

(4) That MCS has not been shown to be a scientifically reliable or medically valid clinical diagnosis.

Court Findings of Fact, Conclusions of Law and Judgment for the Defendants, July 18, 1999.

"*An individual whose home was treated developed symptoms consistent with organophosphate poisoning.*"

The Agency's report does not indicate whether Dr. Wagner provided any coherent evidence organophosphate poisoning had occurred. What is meant by "symptoms consistent with organophosphate poisoning?" Nausea and vomiting are consistent with organophosphate poisoning, but also with influenza, carbon monoxide poisoning, food poisoning, and viral gastroenteritis. Did this patient require hospitalization? Did he or she receive antidotal treatment with atropine or pralidoxime? Were plasma or red blood cell cholinesterase levels depressed? Without such information, this sort of anecdote should not appear in a regulatory document.

Page 11, first full paragraph. "*This is another episode of acute illness developing in children as the result of pesticide treatment to a school in which the formulation was applied while children and teachers were in the building.*"

Once again, this type of anecdotal information is not helpful in the absence of details regarding environmental measurements, details of clinical illness (including cholinesterase levels), and justification for such recommendations to "put in an entirely new heat duct system."

This entire section of "case reports" consists of nothing more than unvalidated claims of untenable events. If crucial information are available in the form of case reports to share with the medical community about what appear to be significant and unwarranted risks of chlorpyrifos, it should not be kept within the EPA, but rather submitted to peer review for publication in a reputable journal.

Page 12, multiple chemical sensitivities. "*Various hypotheses have been advanced to explain multiple chemical sensitivities.*"

MCS is uniformly viewed by the scientific and medical community as baseless (see the statements of the AMA, ACOEM, and AAAAI earlier in this document). To suggest that more research is needed to "resolve the controversy about causal mechanisms" is to suggest that MCS exists. These organizations and many court decisions have made it clear there is no plausible evidence MCS exists as a disease or recognizable clinical syndrome. A syndrome that does not exist cannot have a causal mechanism.

Even proponents of MCS have recognized that MCS is, at best, a controversial and unproven theory lacking in scientific basis. Ashford, N. and Miller, C., "Clinical Exposures: Low Levels and High Stakes," Van Nostrand Rynhold, 111 and 125 (1991).

Page 12, literature on chronic effects.

This discussion mixes cases of neurological dysfunction following documented acute organophosphate poisoning with claims of "neurobehavioral damage" reported in the lay literature (Rouche 1988). The article by Kaplan et al. was reviewed by the Blue Ribbon Epidemiology Committee and dismissed as unconvincing. In Kaplan, four of the cases were members of a single

family. This family was involved in considerable litigation and their testimony and medical records have been reviewed. The father was a diabetic and a reported alcoholic, with a court record detailing abusive behavior towards the family. The other family members were reported to have been subjected to a number of premorbid difficulties including alleged sexual abuse, financial problems, and previous arrests. One of the children reportedly performed poorly in school prior to the exposure. These psychological stresses along with the father's physical condition were such that the cognitive and neurological dysfunction described in the paper would not be unexpected, irrespective of potential exposure to chlorpyrifos.

The case of Rosenthal and Cameron is a case of MCS, which has not been scientifically linked to chlorpyrifos or any other chemical. Rouche 1988 is unsubstantiated, not peer reviewed, and thus has no place in a scientific evaluation. The abnormalities in the Thrasher study could not be reproduced by other labs.

The study by Steenland, et al. (1994) identified 17 workers exposed to chlorpyrifos. The investigators concluded that there are long-term neurological effects of organophosphate poisoning. In an analysis limited to individuals primarily exposed to chlorpyrifos, two tests attained statistical significance: peroneal motor nerve conduction velocity and ulnar sensory amplitude. When the analyses included cases with at least some exposure to chlorpyrifos, worse vibrotactile sensitivity (among the definitely poisoned) was significant for the finger but not the toe. Because evidence for axonal degeneration is typically observed in the long nerves of the legs (peroneal and sural) before those of the arm (median and ulnar) and in sensory nerves before motor nerves, the study's results were not biologically plausible. Not only are the above findings incompatible with the pathology of true nerve damage, they are also inconsistent with each other. These inconsistencies suggest that the observed differences between exposed and unexposed subjects are not explained by exposure to chlorpyrifos.

There is no question severe organophosphate poisoning caused by massive expsoure, where generalized seizures and brain swelling sometimes occur, may be followed by long-term

neurological dysfunction, including sequelae typical of the central nervous system hypoxia. The occurrence of long term neurobehavioral damage in the absence of acute poisoning remains speculative at best.

2. DAS Product Stewardship Program and FIFRA 6(a)(2) Reporting

Since 1996 DAS has operated an expanded product stewardship program which includes 24 hour a day support to consumers or health professionals regarding reported exposures to its products. This program was initiated as part of the "10 Point Plan" agreed to by both the Agency and DAS and is provided through independent experts in Poison Control that are also affiliated with the University of Minnesota.

Calls made to DAS regarding exposure to a DAS product are directly routed to an independent poison control center where poison information specialists and other professional toxicology staff respond to the incident. As part of this contracted service, DAS has provided funding to ensure that the PC staff makes every effort to gather thorough, complete, and product specific documentation for every incident reported. This is in contrast to the type of data and level of detail collected in public PC practice and submitted to the AAPCC to be included in TESS. In addition to an expanded set of data elements, the PC provides DAS with all narrative case notes and documentation, which has also been made available to EPA upon request, and, more recently, as a standard of practice for all DAS FIFRA 6(a)(2) submissions requiring "single incident" reporting. Data collected through this system is subjected to three levels of quality assurance involving senior clinical toxicology staff beyond the initial review provided by the poison information specialist handling and documenting the case.

Despite the fact that the new FIFRA 6(a)(2) submission guidelines do not *require* any investigation on the part of the registrant into any of the incident details provided by those reporting incidents, DAS has invested substantial resources and funding to ensure that as much detail and investigation as can be provided through telephone based reporting be performed. In

DAS has made two presentations of annual summaries of this data to EPA in addition to written reports. During this last year, full case details including case notes have been provided to the Agency. A third presentation to discuss last year's data was planned when the reregistration document was provided to DAS for comment.

None of the data collected and reported through the FIFRA 6(a)(2) process regarding chlorpyrifos has been tabulated or presented in the preliminary human health risk assessment.

This includes data provided through the DAS product stewardship initiative as agreed upon by DAS and the Agency in the "10 Point Plan." Interestingly enough, this includes exclusion of any FIFRA 6(a)(2) data submitted on chlorpyrifos from any registrant that would support the EPA's chlorpyrifos risk assessment.

DAS has incurred considerable expense in providing comprehensive product stewardship and post-market surveillance of its products. DAS has incurred considerable expense in making every effort to cooperate and share information with the Agency regarding any allegation of adverse effects to any of its products. Although the Agency has had the raw data from our submissions during this last year, they have chosen not to summarize that information.

What is more perplexing is the fact that the nature of calls made to the DAS emergency poison information center are identical to those received in the public poison center environment. The greatest difference is the extent and level of detail involved in the DAS investigation and collection of data regarding these incidents to the greatest extent possible given the limitations of telephone based incident reporting. If this data contains insufficient detail to draw any conclusions related to risk, how can the Agency rely so heavily on TESS derived data to determine the unreasonable risk purported to be associated with chlorpyrifos? This simply makes no sense whatsoever.

As an example, a brief summary of human incident data collected through the DAS PC and submitted in detail during the first year of the recently updated FIFRA 6(a)(2) process (i.e., June 17, 1998 through June 30, 1999) demonstrated the following:

- 43 incidents reportedly involved chlorpyrifos as a single substance or product in an alleged exposure resulting in adverse effects of an H-C (moderate) or greater outcome.
- All but one of these incidents involved adults.
- Of these 43 incidents all but two were classified as category H-C (moderate).
- Two incidents were classified as H-B (major).

Case 1: The first incident was the result of gross negligence in that a concentrated chlorpyrifos product was placed in a "baby bottle," stored in a refrigerator and subsequently fed to a child. The child was admitted for medical care, treated with specific antidote, made a full recovery and was discharged two days after the event.

Case 2: The second incident involved information provided by a friend of a patient who reported that the patient "may" have come in contact with chlorpyrifos during a recent application. The patient subsequently developed muscle weakness and an elevated cpk (>3000 IU) and was under the care of physician. Cholinesterase testing was offered through the patient's friend but neither the patient nor her physician ever contacted the DAS PC for assistance. Subsequent calls to the friend for follow-up were unanswered.

All cases were reviewed by a team of independent toxicologists to determine consistency of the incident circumstances and reported signs and symptoms of exposure as compared to the established toxicology profile of chlorpyrifos and/or organophosphates as a class. Clinical effects were coded as "consistent," "inconsistent" or "unknown" (consistency indeterminable).

Route	**Total number of patients**	***x* (H-C) Moderate Category**	***x* (H-B) Major Category**	**% consistent (expected) symptoms**	**% Unknown (consistency indeterminable)**	**% Positive cholinesterase (confirmed exposure)**	**% Reporting Odor**
Unknown (presumed environmental)	36	35	1	0%	6%	0%	44%
Ingestion	1	0	1	100%	0%	100%	NA
Ocular	1	1	0	100%	0%	NA	NA
Dermal	5	5	0	0%	0%	0%	NA

- Two of the "dermal" exposures were believed to be the same patient reported secondhand by two unrelated individuals. The patient alleged to these individuals to have had incidental dermal contact with a Christmas tree six months after it had been reportedly sprayed with an unknown Dursban product. The patient reported symptoms lasting months after this incident.

- Only two of the 43 cases reported signs and symptoms deemed consistent with the toxicology profile or the nature of the exposure. These included the earlier cited pediatric patient and, secondly, an adult with an ocular exposure which resulted in an apparent corneal abrasion believed secondary to the rinse procedure as chlorpyrifos is not corrosive.
- Virtually all of these patients were referred to their primary medical provider for medical evaluation. Patients were routinely offered cholinesterase testing through their physicians to aid in exposure confirmation. Physicians elected to perform cholinesterase testing in 10 of the patients, with all but one (the pediatric ingestion case) showing negative results. One additional patient with a suspected allergy to chlorpyrifos underwent allergy patch testing, with negative results. Even in those cases where a reasonable benefit of doubt was applied to the consistency rating (unknown if consistent), there was no cholinesterase testing performed to aid in the exposure confirmation.

A full summary of the three-year incident monitoring experience is being prepared for publication. An important comparison of data collected through this system and that of data reported through the general public poison center reporting system (i.e., TESS) is that the nature of the inquiries and the ability of the patient to provide quality information is sometimes elusive in both systems. In the case of the DAS surveillance system, these cases of consequence have been investigated as thoroughly as possible with the added benefit of laboratory testing to confirm exposure. The majority of patients in our series either refused the offer of laboratory confirmation assistance at their own choice or that of their physician. Since laboratory confirmation is neither offered nor recorded by the public poison centers the number of true chlorpyrifos “poisonings” reported through public poison center system is still unknown.

F. Biomonitoring, Cumulative Exposure and Aggregate Risk Assessment on Chlorpyrifos

1. Biomonitoring Studies

In the EPA documents on “Agricultural and Occupational Exposure Assessment” and the Occupational/Residential Handler and Post-Application Residential Risk Assessment,” a number

of urinary 3,5,6-trichloro-2-pyridinol biomonitoring studies were cited and used to calculate exposures to chlorpyrifos. It is important, however, to understand what TCP measurements really tell us about a person's exposure to chlorpyrifos.

In both humans and the environment, chlorpyrifos and chlorpyrifos-methyl are readily degraded or metabolized into the primary metabolite 3,5,6-trichloro-2-pyridinol, commonly referred to as TCP. TCP can, and is, often used in biomonitoring studies as an indicator of chlorpyrifos exposure. Although TCP levels measured in study participants' urine can be used to estimate *potential* chlorpyrifos exposure levels, some portion of these measured levels is likely due to exposure to chlorpyrifos-methyl and/or TCP itself. Therefore, direct extrapolations from measured TCP levels back to possible chlorpyrifos exposures should be recognized as very conservative, worst-case estimates, and the potential contribution to TCP levels from these other sources should be excluded when drawing conclusions about possible health risks.

2. Cumulative Exposure and Risk Assessment on Chlorpyrifos

EPA proposed to conduct a cumulative risk assessment on OP pesticides, including chlorpyrifos, in the near future. Furthermore, EPA assumes OP pesticides have a common mechanism of toxicity. DAS disagrees that all OP pesticides cause adverse effects with a common mechanism of toxicity. While all OP pesticides may inhibit AChE activity, there are other mechanisms (PK and PD events) operating in the body that affect the toxicity of OP pesticides (Pope, 1999; SAP, 1998). Data have shown chlorpyrifos is different than other OP pesticides (e.g., parathion). There are PK and PD actions operating which moderate (i.e., lower) the toxicity induced by chlorpyrifos.

In contrast to other OP pesticides, several investigators have demonstrated that inhibition of brain AChE by chlorpyrifos does not correlate with toxicity (i.e., lower toxicity) as might be expected. The divergence in the relationship between potency to inhibit AChE and anticipated toxicity is illustrated in studies with intact animals. The chlorpyrifos ED_{50} for inhibition of brain AChE in rats was approximately 16% of the chlorpyrifos maximum tolerated dose (MTD), while the

parathion ED_{50} was approximately 38% of the parathion MTD (Pope et al., 1992). In addition, fewer signs of toxicity were noted in chlorpyrifos-treated rats than parathion-treated, even though chlorpyrifos treatment caused greater inhibition of brain AChE (Chaudhuri et al., 1993). These studies show that, in addition to inhibition of AChE, there are PK and PD action(s) operating which moderate (i.e., lower) the toxicity induced by chlorpyrifos.

EPA sponsored the International Life Sciences Institute (ILSI) to conduct a study on the common mechanism of toxicity of OP pesticides and the final published report (Mileson et al., 1998) was submitted to the SAP in March 1998 for the SAP's review. The SAP raised a number of concerns (SAP 1998). SAP members noted the limited charge of the ILSI working group in determining if OP pesticides operate by a common mechanism of toxicity. Considerations of PK and PD were not included in the charge to the working group. The SAP stated in their report (SAP, 1998):

> "*The [ILSI] Working Group operated using a very narrow definition of mechanism of toxicity, which involved the events following interaction of the pesticide with the target molecule. The narrow scope of the charge to the Working Group precluded the consideration of how PK and PD factors contribute to the overall toxic response to any given compound.*"

Based on the available data, chlorpyrifos has been shown to be different than other OP pesticides. There are PK and PD actions operating in the body which lower the toxicity induced by chlorpyrifos.

3. Aggregate Risk Assessment on Chlorpyrifos

The EPA states an aggregate risk estimate was not conducted for any duration because, based on their assessments, some of the acute dietary and chronic dietary exposures, and the total residential MOEs for all the residential postapplication exposure scenarios, except mosquitocide use, alone exceed HED's level of concern. As outlined in the appropriate sections of this response, DAS has provided data and other information which show the assessments conducted contain errors which cause exposures to be significantly overestimated. DAS believes more realistic assessments show exposures are within acceptable levels. DAS does, however, recognize

there is no scientifically-accepted, finalized methodology from the Agency on conducting aggregate assessments. DAS has previously submitted an aggregate assessment showing exposures from all uses are within acceptable levels and are awaiting Agency comments on this assessment. DAS also is aware EPA is working on development of methods for assessing aggregate risk (HRI project) and would welcome the opportunity to work with the Agency in conducting a scientifically-sound, realistic aggregate assessment when this technology is available.

III. Information Submitted with DAS's Comments

DAS has identified additional information that is being submitted along with this document and its appendices. These documents are listed below:

Elder, A.; Johnson, S. V.; Dolibois, R. J., "National Plant Board, U.S. Domestic Japanese Beetle

Mar-Quest Research Inc., "Qualitative Research on the Labeled Application and Use of Chlorpyrifos by Professional Markets," 1999, unpublished report for Dow AgroSciences.

USDA (1995). "Imported Fire Ant, Quarantine Treatments for Nursery Stock and Other Regulated Articles," USDA, Animal and Plant Health Inspection Service, Plant Protection and Quarantine.

Wolt, J. D., "Exposure Endpoint Selection in Acute Dietary Risk Assessment," *Regul. Toxicol. Pharmacol.*, **29**:279-286, 1999.

IV. Additional Planned Studies

Currently, DAS is conducting, in partnership with four other companies, a community water system surface drinking water monitoring study for five OP insecticides and their major degradation products in the United States. Chlorpyrifos is one of the compounds in the study. We anticipate study completion by the end of calendar year 2000. Tolerance Reassessment Advisory Committee (TRAC), along with other interested parties, has called upon the EPA to utilize the best information available in implementation of FQPA. The EPA should recognize the limitations imposed by the conservative nature of the currently available data, which is associated

primarily with source water, not drinking water, and we encourage the Agency to utilize this new data to refine the assessments when it becomes available.

The repeated exposure neurotoxicity study of sensory electrophysiology with chlorpyrifos that was mentioned in the Toxicology Chapter for chlorpyrifos has been delayed due to resource constraints (equipment and people) and, at present, there is no definite start date.

V. References

AIHC, *Exposure Factors Sourcebook*, American Industrial Health Council, Suite 760, 2001, Pennsylvania Avenue, NW, Washington, D.C., 1994.

Albers, J. W.; Cole, P.; Greenberg, R. S.; Mandel, J. S.; Monson, R. R.; Ross, J. H.; Snodgrass, W. R.; Spurgeon, A.; van Gemert, M., "Analysis of Chlorpyrifos Exposure and Human Health: *J. Tox. Environ. Health*, Part B, **2**(4):101-124, 1999.

AMA Council on Scientific Affairs, "Clinical Ecology: Position Statement of the American *JAMA*, **268**:3465-3467, 1992.

Amitai, G.; Moorad, D.; Adani, R.; Doctor, B. P., "Inhibition of Acetylcholinesterase and Butyrylcholinesterase by Chlorpyrifos-Oxon," *Biochem. Pharmacol.* **56:**293-299, 1998.

Appel, A. G.; Reid, B. L., "Sampling German Cockroach Field Populations: Theory, Reliability In: Robinson, W. H, ed, *Proceedings of the National Conference on Urban Entomology*, pp 51-65, 1992.

Barnes, D. G.; Dourson, M. L., "Reference Dose (RfD): Description and Use in Health Risk *Regul. Toxicol. Pharmacol.* **8:**471-486, 1988.

Baroncelli, S.; Karrer, D.; Turiliazzi, P.G., "Oral Bis(tri-n-butyltin) Oxide in Pregnant Mice. I. Potential Influence of Maternal Behavior on Postnatal Mortality," *J. Toxocol. Environ. Hlth.* **46**:355-367, 1995.

Barrett, S.; Gots, R. E., *Chemical Sensitivity. The Truth About Environmental Illness,* Prometheus Books, Amherst, NY, 212 pp, 1998.

Bolles, H. G.; Dixon-White, H. E.; Peterson, R. K.; Tomerlin, J. R.; Day, Jr., E. W.; Oliver, G. R., "U.S. Market Basket Study to Determine Residues of the Insecticide Chlorpyrifos," *J. Agricultural and Food Chemistry*, **47**:1817-1822, 1999.

Boobis, A., "Toxicological - The Derivation of the Acute RfD," In *International Conference on Pesticide Residues Variability and Acute Dietary Risk Assessment,* York, UK, 1-3 December, 1998.

Brenner, F. E., Bond, G. G.; Mclaren, E. A.; Greene, S.; Cook, R. R., "Morbidity Among Employees Engaged in the Manufacture or Formulation of Chlorpyrifos," *British J. Indust. Med.*, **46**:133-137, 1989.

Brzak, K. A.; Harms, D. W.; Bartels, M. J.; Nolan, R. J., "Determination of Chlorpyrifos, Chlorpyrifos oxon and 3,5,6-trichloro-2-pyridinol in Rat and Human Blood," *J. Anal. Toxicol*. **22**:203-230, 1998.

Burns, C. J.; Cartmill, J. B.; Powers, B. S.; Lee, M. K., "Update of the Morbidity Experience Among Employees Potentially Exposed to Chlorpyrifos," *Occup. Environ. Med.* **55**:6-70, 1998.

Byrne, S. L.; Cook, W. L.; Meitl, T. J.; Shurdut, B. A.; Saunders, D. G.; Lardie, T. S.; Powers, F. L., "Residential Exposure to Chlorpyrifos from Reentry to Structures Treated with Crack and Crevice and Spot Applications of Dursban Pro," GH-C 4553 (MRID 44458201), 1998, unpublished report of Dow AgroSciences.

Capodicasa, E.; Scapellato, M. L.; Moretto, A.; Caroldi, S.; Lotti, M., "Chlorpyrifos-Induced
Arch. Toxicol. **65**:150-155, 1991.

Carlock, L. L.; Chen, W. L.; Gordon, E. B., "Regulating and Assessing Risks of Cholinesterase-Inhibiting Pesticides: Divergent Approaches and Interpretations," *J. Toxicol. Environ. Health*, Part B, **2**:105-160, 1999.

Chapman, N., "Request for Comments OP Pesticide: Azinphos-Methyl; Risk Assessments," 1999.

Chakraborti, T. K.; Farrat, J. D.; Pope, C. N., "Comparative Neurochemical and Neurobehavioral Effects of Repeated Chlorpyrifos Exposures in Young and Adult Rats," *Pharmacol. Biochem. Behavior* **46**:219-224, 1993.

Chaudhuri, J.; Chakraborti, T. K.; Chanda, S; Pope, C. N., "Differential Modulation of Organophosphorus-Sensitive Muscarinic Receptors in Rat Brain by Parathion and Chlorpyrifos," *J. Biochem. Toxicol.* **8**:207-216, 1993.

Chen, W. L.; Sheets, J. J.; Nolan, R. J.; Mattsson, J. L., "Human Red Blood Cell Acetylcholinesterase Inhibition as the Appropriate and Conservative Surrogate Endpoint for Establishing Chlorpyrifos Reference Dose," *Reg. Tox. Pharm.* **29:**15-22, 1999.

Chmiel, J.; Garafalo, M. J., "A Study on the Effects of Chlorpyrifos-methyl on Plasma and Erythrocyte Cholinesterase Activity in Human Subjects During Subacute Oral Administration," GH-RC 61 (MRID 00030755, 00043235), 1975, unpublished report of The Dow Chemical Company.

Christensen, B. R.; Dando, C. L., "Historical Occurrence of Acephate, Azinphos-methyl, Chlorpyrifos, Diazinon and Malathion in Waters of the United States, 1990-1997," Project No. 006 (MRID 44845201), 1999, unpublished report of En*fate, Plymouth, MN, submitted to U.S. EPA by Bayer Corporation.

Clegg, D. J.; van Gemert, M., "Determination of the Reference Dose for Chlorpyrifos: Proceedings of an Expert Panel," *J. Toxicol. Environ. Health*, Part B, **2**:211-255, 1999.

Clegg, D. J.; van Gemert, M., "Expert Panel Report of Human Studies on Chlorpyrifos and/or Other Organophosphate Exposures," *J. Tox. Environ. Health*, Part B, **2**:257-279, 1999.

Comments by the FQPA Implementation Working Group to Office of Pesticide Programs' Science Policies titled: "Standard Operating Procedures (SOPs) for Residential Exposure Assessment" and "Framework for Assessing Non-Occupational, Non-Dietary (Residential) Exposure to Pesticides" 64 FR 162, January 4, 1999: Docket Nos. OPP-00578 and OPP-0579, March 1999, www.fqpa.com/index.cfm.

Conolly, R. B.; Beck, B. D.; Goodman, J. I., "Stimulating Research to Improve the Scientific *Toxicol. Sci* **49**:1-4, 1999.

Coulston, F.; Goldberg, L.; Griffin, T. B., "Analysis of Dowco 179 in Humans," HET-44793-(48)B (MRID 00095175), 1972, unpublished report of The Dow Chemical Company.

Coulston, F.; Golberg, L.; Abraham, R.; Benitz, K. F.; Griffin, T. B.; Norvell, M., "Final Report on Safety Evaluation and Metabolic Studies on Dowco 179," 1971, unpublished report of The Dow Chemical Company.

Coulston, F.; Griffin, T. B., "Study of Chlorpyrifos-methyl in Human Volunteers," GH-RC 27 (MRID 00030754, 00043238), 1975, unpublished report of The Dow Chemical Company.

Deacon, M. M.; Murray, J. S.; Pilny, M. K.; Rao, K. S.; Dittenber, D. A.; Hanley, Jr, T. R.; John, J. A., "Embryotoxicity and Fetotoxicity of Orally Administered Chlorpyrifos in Mice," *Toxicol. Appl. Pharmacol*. **54**:31-40, 1980.

Dourson, M. L.; Stara, J. F., "Regulatory History and Experimental Support of Uncertainty *Regul. Toxicol. Pharmacol.* **3:**224-238, 1983.

Dourson, M. L.; Felter, S. P.; Robinson, D., "Evolution of Science-Based Uncertainty Factors in *Reg. Toxicol. App. Pharmacol.* **24:**108-120, 1996.

Elder, A.; Johnson, S. V.; Dolibois, R. J., "National Plant Board, U.S. Domestic Japanese Beetle

Francis, M.; Shurdut, B. A., "Chlorpyrifos Integrated Exposure Assessment," GH-C 4192 (MRID 44104001), 1996, unpublished report of Dow AgroSciences LLC.

Gibson, J. E.; Chen, W. L.; Peterson, R. K. D., "How to Determine if an Additional 10x Safety Factor is Needed for Chemicals: A Case Study with Chlorpyrifos," *Tox. Sci.,* **48**:117-122, 1999.

Goldman, L. R., EPA Letter to Mr. John Hagaman of DowElanco, January 14, 1997.

Griffin, P.; Mason, H.; Heywood, K.; Cocker, J., Personal communication, submitted to Occupation and Environmental Medicine, 1999.

Herrman, J. L., "Acute Intake Assessment," In *International Conference on Pesticide Residues Variability and Acute Dietary Risk Assessment,* York, UK, 1-3 December, 1998.

Hoberman, A. M., "Developmental Neurotoxicity Study of Chlorpyrifos Administered Orally via Gavage to Crl:CD®BR VAF/Plus® Presumed Pregnant Rats," 304-001 (MRID 44556901), 1998, unpublished report of Dow AgroSciences LLC.

Hoberman, A. M., "Supplement 2. Developmental Neurotoxicity Study of Chlorpyrifos Administered Orally via Gavage to Crl:CD®BR VAF/Plus® Presumed Pregnant Rats," Argus 304-001S (MRID 44787301), 1999, unpublished report of Dow AgroSciences LLC.

Kai, S.; Kohmura, H.; Ishikawa, K.; Kodota, T.; Kawano, S.; Takahashi, N. "Effects of Butorphanol Tartrate on Cross-Fostering in Rats," *Nippon Yakurigaky Zashi* **83**:115-122, 1982.

Kisicki, J. C.; Seip, C. W.; Combs, M. L., "A Rising Dose Toxicology Study to Determine the No Observable Effect Levels (NOEL) for Erythrocyte Acetylcholinesterase (AChE) Inhibition and Cholinergic Signs and Symptoms of Chlorpyrifos at Three Dose Levels," DR K-044793-284 (MRID 44811002), 1999, unpublished report of Dow AgroSciences LLC.

Knizner, S. A., "Revised Product and Residue Chemistry Chapters of the HED Chapter of the RED," U.S. EPA, Health Effects Division, May 25, 1999.

Lashor, J. C., "Report of the Presidential Advisory Committee on Gulf War Veteran's Illnesses," Washington, DC: U.S. Government Printing Office, 1996.

Litovitz, T. L.; Smilkstein, M.; Felberg, L.; Klein-Schwartz, W.; Berlin, R.; Morgan, J. L., "1996 Annual Report of the American Association of Poison Control Center Toxic Exposure Surveillance System," *Am J Emerg Med*, **15**:447-500, 1997.

Liu, J.; Olivier, K.; Pope, C.N., "Comparative Neurochemcial Effects of Repeated Methyl Paration or Chlorpyrifos Exposure in Neonatal and Adult Rats," *Toxicol. Appl. Pharmacol.* **158**:186-196, 1999.

Lotti, M., "Cholinesterase Inhibition: Complexities in Interpretation," *Clin. Chem.* **41:**1814-1818, 1995.

Makris, S.; Raffaele, K.; Sette, W.; Seed, J., "A Rretrospective Analysis of Twelve Developmental Neurotoxicity Studies Submitted to the USEPA Office of Prevention, Pesticides, and toxic Substances," draft 11/12/98.

Mar-Quest Research Inc., "Qualitative Research on the Labeled Application and Use of Chlorpyrifos by Professional Markets," 1999, unpublished report for Dow AgroSciences.

Mattsson, J. L.; Spencer, P. J.; Brzak, K. A.; Maurissen, J. P.; Zablotny, C. L., "Effects of Chlorpyrifos Administered via Gavage to CD Rats During Gestation and Lactation on Plasma, Erythrocyte, Heart and Brain Cholinesterase, and Analytical Determination of Chlorpyrifos and Metabolites," 971162 (MRID 44648101), 1998, unpublished report of Dow AgroSciences LLC.

McCollister, S. B.; Kociba, R. J.; Humiston, C. G.; McCollister, D. D.; Gehring, P .J., "Studies of the Acute and Long-Term Oral Toxicity of Chlorpyrifos (O, O-diethyl O-3,5,6-trichloro-2-pyridyl phosphorothioate)," *Food Cosmet. Toxicol.* **12:**45-61, 1974.

Mileson, B. E.; Chambers, J. E.; Chen, W. L.; Dettbarn, W.; Elrich, M.; Eldefrawi, A .T.; Gaylor, D. W.; Hamernik, K.; Hodgson, E.; Karczmar, A. G.; Padilla, S.; Pope, C. N.; Richardson, R. J.; Saunders, D. R.; Sheets, L. P.; Sultatos, L. G.; Wallace, K.B., "Common Mechanism of Toxicity: A Case Study of Organophosphorus Pesticides," *Tox. Sci.*, **41**:8-20, 1998.

National Gardening Association, "National Gardening Survey," 1997-1998.

Nolan, R. J.; Rick, D. L.; Freshour, N. L.; Saunders, J. H., "Chlorpyrifos Pharmacokinetics in *Toxicol. Appl. Pharmacol.* **73**:8-15, 1984 (also MRID 00124144).

Nolan, R. J.; Freshour, N. L.; Rick, D. L., "Chlorpyrifos: Pharmacokinetics in Human Volunteers Following Single Oral and Dermal Doses," K-44793-61 (MRID 00124144), 1982, unpublished report of The Dow Chemical Company.

Oliver, G. R., "Is the Use of 99.9th Percentile for Regulatory Decision-Making Under FQPA *Risk Policy Report,* **16(4)**:32-34, 1999.

Poletika, N. N.; Robb, C. K., "A Monitoring Study to Characterize Chlorpyrifos Concentration Patterns and Ecological Risk in an Agriculturally Dominated Tributary of the San Joaquin River," GH-C 4854 (MRID 44711601), 1998, unpublished report of Dow AgroSciences.

Poletika, N. N.; Blewett, T. C.; Chambers, D. M.; Cryer, S. A.; Fontaine, D. D.; Havens, P. L.; Mayes, M. A.; Mortensen, S. R.; Shaw, M. C.; Woodburn, K. B., "Dow AgroSciences' Response to U.S. EPA's Draft Reregistration Eligibility Science Chapter for Chlorpyrifos, Fate and Environmental Risk Assessment Chapter Dated November 24, 1998," GH-C 4873 (MRID 44736901), 1999, unpublished report of Dow AgroSciences.

Pope, C. N., "Organophosphorus Pesticides: Do They All Have the Same Mechanism of
J. Tox. Environ. Health, Part B, **2**:161-181, 1999.

Pope, C.N.; Liu, J., "Age-Related Differences Insensitivity to Organophosphorous Pesticides," *Environ. Toxicol. Pharmacol*. **4**:309-314, 1997.

Pope, C. N.; Charkraborti, T. K., "Dose-Related Inhibition of Brain and Plasma Cholinesterase in Neonatal and Adult Rats Following Sublethal Organophosphate Exposures," *Toxicology*, **73**:35-43, 1992.

Positions of the American Academy of Allergy, Asthma and Immunology: Clinical Ecology, *J Allergy Clin Immunol*, **78**:269-277, 1986.

Residential Exposure Assessment Spreadsheet Tool (REx), developed by the OP Case Study Group, 1999.

Richardson, R. J.; Moore, T. B., Kayyali, U. S.; Randal, J. C., "Chlorpyrifos: Assessment of Potential for Delayed Neurotoxicity by Repeated Dosing of Adult Hens with Monitoring of Brain Acetylcholinesterase, Brain and Lymphocyte Neurotoxic Esterase and Plasma Butyrylcholinesterase Activities," *Fundam. Appl. Toxicol*. **21**:89-96, 1993.

Schardein, J. L.; Scialli, A. R, "The Legislation of Toxicologic Safety Factors: the Food Quality Protection Act with Chlorpyrifos as a Test Case," *Repro. Toxicol*. **13**(1):1-14, 1999.

Scientific Advisory Panel (SAP), February 1999 Meeting of the Scientific Advisory Panel, Arlington, VA, 1999.

Scientific Advisory Panel (SAP), "Final Report of the FIFRA Scientific Advisory Panel Meeting held March 24-25, 1998," Arlington, VA, March 24-25, 1998.

Scientific Advisory Panel (SAP), "SAP Report No. 99-03," FIFRA Scientific Advisory Panel Meeting, Arlington, VA, May 25-27, 1999.

Stafford, L. E.; Robb, C. K., "Determination of Dislodgeable Foliar Residues on Turf Treated with Formulations Containing Chlorpyrifos," GH-C 4847 (MRID 44829601), 1999, unpublished report of Dow AgroSciences.

Staudenmeyer, H., *Environmental Illness: Myth and Reality*, Lewis Publishers, Boca Raton, FL, 376 pp, 1999.

Szabo, J. R.; Young, J. T.; Grandjean, M., "Chlorpyrifos: 13-Week Dietary Toxicity Study in Fischer-344 Rats," K-044793-071 (MRID 40952801), 1988, unpublished report of The Dow Chemical Company.

Thomas, J. D.; Chambers, D. M., "An Analysis of Factors Involved in Suspected Well Contaminations by Chlorpyrifos-Based Termiticide Emulsions (Dursban TC, Equity Termiticide) Based on Water Incident Survey and Analytical Data," DERBI 48202 (MRID 44235001), 1997, unpublished report of Dow AgroSciences.

USDA (1995). "Imported Fire Ant, Quarantine Treatments for Nursery Stock and Other Regulated Articles," USDA, Animal and Plant Health Inspection Service, Plant Protection and Quarantine.

U.S. EPA, "Pesticide Product Label System," February 1994, update 4/28/99.

U.S. EPA (1998). "Proposed Threshold of Regulation Policy Defining When a Food Use Does Not Require a Tolerance" (EPA Draft 11/30/98), Office of Prevention, Pesticides and Toxic Substances, http://www.epa.gov.

Vaccaro, J.; Bohl, R.; Skowronski, B.; Moribito, P., "Airborne Chlorpyrifos Concentrations Measured During and Following Applications of Dursban TC Insecticide to Residential Dwellings," GH-P 1310 (MRID 40094001), 1987, unpublished report of The Dow Chemical Company.

Vaccaro, J.; Nolan, R. J.; Hugo, J.; McNett ,D., "Chlorpyrifos: Exposure to Adults and Children Upon Reentry to Domestic Lawns, Following Treatment with a Chlorpyrifos-Based Mixture," HEH2.1-1-182(121) (MRID 43013501), 1993, unpublished report of DowElanco.

Vaccaro J.; Beard, K.; Maxey, S.; Murphy, P.; Myers, C.; Nolan, R. J.; Ormand, J.; Timchalk, C., "Chlorpyrifos: Exposure to Adults and Children Upon Reentry to Domestic Lawns, Following Treatment with a Chlorpyrifos-Based Granular Insecticide," HEH2.1-1-182(134) (MRID 44167101), 1996, unpublished report of DowElanco.

Wagner, S. L., "Pesticide Illness Surveillance: Review of the National Pesticide Hazard
Am J Ind Med, **18**:307-12, 1990.

Wolt, J. D., "Exposure Endpoint Selection in Acute Dietary Risk Assessment," *Regul. Toxicol. Pharmacol.*, **29**:279-286, 1999.

World Health Organization (WHO), "Principles for the Toxicological Assessment of Pesticide Residues in Food. International Program on Chemical Safety," Geneva, 1990.

Young, J. T.; Grandjean, M., "Chlorpyrifos: 2-Year Chronic Toxicity-Oncogenicity Study in Fischer 344 Rats," K-044793-079 (MRID 40952802), 1988, unpublished report of The Dow Chemical Company.

Appendix A: DAS Calculation of Acute and Chronic RfD Values

There are substantial differences in the approaches taken by the U.S. EPA and by DAS in the risk assessment of humans exposed to chlorpyrifos. These differences lead to marked differences in the resulting hazard assessment and are due to the Agency's use of default values when scientifically-valid studies show these defaults should be abandoned (Conolly et al., 1999; Dourson et al., 1996). For chlorpyrifos, and organophosphates in general, there is a wealth of valid scientific data that indicate many of these conservative defaults should be replaced. DAS feels there is sufficient valid data to replace conservative defaults with the following:

- Scientifically valid human studies exist for chlorpyrifos. When such studies exist, they should take precedence over data from animal studies in setting RfDs for chlorpyrifos (Clegg and van Gemert, 1999; Barnes and Dourson, 1988; Dourson and Stara, 1983; Boobis, 1998; Herrman, 1998).
- Human RBC AChE inhibition data should be used to set RfDs for chlorpyrifos. It is generally accepted that NOELs and RfDs used in a hazard assessment should be based on a measure of toxicity (e.g., cholinergic effects and/or AChE inhibition) and not on a measure of exposure (e.g., BuChE) (Lotti, 1995; Clegg and van Gemert, 1999; Chen, 1999; Carlock et al., 1999).
- When the same endpoint is considered, studies show a similar dose-response and NOELs for chlorpyrifos in humans, non-human primates, dogs, rats and mice. The animal studies strongly support that inhibition of human RBC AChE is the appropriate endpoint for chlorpyrifos hazard evaluation.
- There are sufficient data to conclude that the fetus and neonate are not more sensitive to chlorpyrifos than the adult. Two recent reviews of the relevant literature (Schardein and Scialli, 1999; Gibson et al., 1999) report the same conclusion.
- Acute and chronic RfDs proposed by DAS are consistent with those currently utilized by the WHO, the European Union and Canada (WHO, 1990). Acute RfDs, calculated from RBC AChE inhibition data from human studies were 0.05 mg/kg. Chronic RfDs calculated from RBC AChE inhibition data from human studies were 0.01 mg/kg/day. A recent, comprehensive analysis of the chlorpyrifos human and animal toxicity literature by a panel of

toxicology and medical experts reached the same conclusions as above (Clegg and van Gemert, 1999).

A.1. Human Studies Should Take Precedence Over Animal Studies

A.1.1. U.S. EPA Guidelines State it is Ethically Possible to Conduct Human Laboratory Exposure Studies with Chemicals That Have Neurological Effects That are of Short Duration and are Reversible

> "*Neurotoxicity assessment has an advantage not afforded to the evaluation of other toxic endpoints, such as cancer or reproductive toxicity, in that the effects of some chemicals are short in duration and reversible. This makes it ethically possible to perform human laboratory exposure studies and obtain data relevant to the risk assessment process.*" (U.S. EPA Guidelines for Neurotoxicity Risk Assessment, Federal Register, May 14, 1998, Vol 63, Number 93, pp 26925-26954, Section 3.1.1.4. Human Laboratory Exposure Studies)

Chlorpyrifos is such a chemical. Low-dose effects of chlorpyrifos and chlorpyrifos-methyl are the inhibition of plasma ChE and possibly RBC ChE in the absence of alterations in the function of the nervous system. Because plasma and RBC ChE can be inhibited without clinical effect, and the inhibition is reversible, these enzyme inhibitions meet the U.S. EPA's definition for chemical effects than can be ethically studied in humans.

A.1.2. Appropriately Designed Human Studies Should be Used (Clegg and van Gemert, 1999, p 250)

In the recent International Conference on Pesticide Residues Variability and Acute Dietary Risk Assessment held in York, United Kingdom (UK) on 1-3 December 1998, the conduct of human studies and the use of these data for establishing RfDs and risk assessments were encouraged and endorsed. In a lecture by Dr. John Herrman of WHO, he stated:

> "*The results of studies with [human] volunteers are sometimes available for pesticides that have a known mechanism of toxicity. If the relevant endpoints have been assessed these studies are the most appropriate for allocating a reference dose*." (Herrman, 1998)

Dr. Herrman's position was further supported by Dr. Alan Boobis of the University of London and a member of the UK Advisory Committee on Pesticides. Dr. Boobis, who chaired a work group on the use of human data at the International Conference, concluded:

> "Such [human] data are extremely useful, especially for pesticides that cause acetylcholinesterase inhibition, and such studies are desirable from a scientific point of view when appropriately and ethically performed." (Boobis, 1998)

Indeed, for over 15 years (1984-1999), the U.S. EPA has consistently preferred to use data from human studies over the animal studies to set the acute and chronic RfDs for chlorpyrifos. This preference for the use of human data is also true in EPA for other chemicals (Barnes and Dourson, 1988). In a meeting of the SAP held in February 1999, EPA advanced the use of data from human studies to establish the RfD for aldicarb, an anticholinesterase insecticide. During the deliberations, members of the SAP not only supported the use of human data for establishing an RfD for aldicarb, they further encouraged the conduct of human studies on other anticholinesterase insecticides for the purpose of setting RfDs (SAP, 1999).

A.2. Human RBC AChE Inhibition Should be Used to Regulate Chlorpyrifos

A.2.1. RBC AChE Inhibition is the Appropriate Endpoint from Human Studies

In addition to the obvious axiom that human data take precedence over animal data, there is widespread agreement that inhibition of plasma ChE is not an adverse effect and, therefore, is inappropriate for risk assessment (Clegg and van Gemert, 1999; Carlock et al., 1999; Chen et al., 1999). Similarly, inhibition of RBC AChE is not associated with the nervous system and, therefore, its inhibition should be utilized only in the absence of data on inhibition of brain ChE. Because of the inability to measure brain ChE activity in humans, the necessary default is to use RBC AChE inhibition data when human studies are used to set exposure guidelines.

A.2.2. NOEL Values for Human RBC AChE Inhibition are Available

Chlorpyrifos is diethyl-chlorpyrifos, and chlorpyrifos-methyl is dimethyl-chlorpyrifos. Effects of both compounds on human plasma ChE are similar (and similar for differential sensitivity of

plasma ChE > RBC AChE). Because of the similarity of structure and similarity of effect on plasma and RBC AChE, the human ChE data from five studies are summarized below:

EXPOSURE					ChE INHIBITION		
OP	DOSE mg/kg	DAYS	Males	Females	PLASMA	RBC	STUDY ID
CHP	0.014	27	4	0	-	-	Coulston et al. 1972
CHP	0.03	20	4	0	-	-	Coulston et al. 1972
CHP-M	0.03	27	5	0	-	-	Coulston et al. 1975
CHP	0.1	9	4	0	+(4/4)	-	Coulston et al. 1972
CHP-M	0.1	27	5	0	-	-	Coulston et al. 1975
CHP-M	0.1	21	3	3	-	-	Chmiel et al 1975
CHP-M	0.2	21	(3)[1]	(3)	+(3/6)	-	Chmiel et al 1975
CHP-M	0.3	14	(3)	(3)	+(3/6)	-	Chmiel et al 1975
CHP	0.5	1	6	0	+(6/6)	-	Nolan et al. 1984
CHP	0.5	1	6	6	ND	-	Kisicki et al. 1999
CHP	1.0	1	6	6	ND	-	Kisicki et al. 1999
CHP	2.0	1	6	6	ND	+(1/12)	Kisicki et al. 1999

1. Chmiel et al. (1975) study had sequentially treated three males and three females, first at 0.1 mg/kg/day, then 0.3 mg/kg/day followed by a 28-day recovery period, then at 0.2 mg/kg/day. Males and females were affected equally.

It is apparent from these studies that chlorpyrifos is somewhat more potent than chlorpyrifos-methyl as an inhibitor of plasma ChE. The NOEL for chlorpyrifos for inhibition of plasma ChE was 0.03 mg/kg/day, measured over a period of 20 days, and the NOEL for chlorpyrifos-methyl was 0.1 mg/kg/day for 21 or 27 days. The NOEL for chlorpyrifos for inhibition of RBC ChE was 0.1 mg/kg/day (administered for 9 days), the highest dose tested in humans. A single dose of chlorpyrifos at 2 mg/kg caused inhibition of RBC AChE in one of twelve volunteers, and the single-dose NOEL for RBC AChE inhibition was 1 mg/kg. No inhibition of RBC AChE was noted in 6 volunteers in another study at a single dose of 0.5 mg/kg.

A.3. Human Studies are Well Supported by Scientifically-Valid Animal Studies

One's confidence in the human studies on chlorpyrifos are enhanced because of comparable ChE inhibition in a variety of animal studies conducted in monkeys, dogs, rats and mice. When the same endpoint is considered, these animal studies show the dose-response for chlorpyrifos is similar in these diverse species. Note that plasma ChE is more sensitive to inhibition than RBC

AChE. This difference is due to the greater sensitivity of BuChE to inhibition by chlorpyrifos than AChE (Amitai et al., 1998; Griffin et al., 1999). Unlike rodents, plasma ChE activity in humans and dogs is due almost entirely to BuChE. As a consequence, chlorpyrifos dosages that inhibit human and dog plasma ChE are virtually the same, and are lower than dosages than inhibit RBC AChE. In contrast, rodent plasma has a high level of AChE, which makes rodent plasma ChE less sensitive to inhibition than in humans or dogs. If chlorpyrifos inhibition of rodent plasma ChE were corrected for the high level of plasma AChE, then the dosages that inhibit rodent plasma ChE would be very similar to the dosages that inhibit human and dog plasma ChE.

The most appropriate endpoint for NOEL determination is an adverse effect. Although not an adverse effect *per se*, a substantial decrease in brain AChE is a common surrogate of an adverse effect, and is an appropriate endpoint for NOEL determinations in animals. Due to the inability to evaluate brain AChE activity in humans, it is necessary to use the next most reasonable surrogate which is RBC AChE. The similarity in the dose response for RBC AChE inhibition in humans, non-human primates, dogs and rodents, measured during a wide variety of exposure conditions, provides strong support to the usefulness of the human RBC AChE inhibition data.

(note: NOELs need to be interpreted in context of dose intervals. (≥) signals a 10x or greater dose interval.)				NOEL FOR ChE INHIBITION			
OP	SPECIES	DOSE (mg/kg)	DAYS	PLASMA	RBC	BRAIN	Reference
CHP	Human	0.5	1	inhibited	≥0.5	Not done	Nolan et al., 1984
CHP	Human	0.5, 1.0, 2.0	1	Not done	1.0	Not done	Coulston et al. 1972
CHP	Human	0.014, 0.03, 0.10	27/20/9	0.03	≥0.1	Not done	Coulston et al. 1972
CHP	Monkey	0.08, 0.4, 2.0	6 mo.	0.08 inhibited	0.08	≥2	Coulston et al. 1971
CHP	Dog	0.01, 0.03, 0.1, 1, 3	<2 yr	0.03	≥0.1	1	McCollister et al., 1974
CHP	Rat	0.05, 0.1, 1, 10	2 yr	≥0.1	≥0.1	≥1	Young et al., 1988
CHP	Rat	0.1, 1, 5, 15	90	≥0.1	≥0.1	1	Szabo et al., 1988
CHP	Mouse	0.1, 1, 10	9	≥0.1	≥0.1	Not done	Deacon et al., 1980

[c]Doses are approximate (from ppm estimates) and are an average of male and females doses.

A.4. Existing Studies Indicate a Lack of Increased Sensitivity of the Young

Schardein and Scialli (1999) reported a lack of increased sensitivity of the young to chlorpyrifos after a review of the relevant literature. The objective of this review was to evaluate the need, or lack thereof, to retain the additional 10x safety factor required by the FQPA. It was concluded "there is no scientific rationale for the application of an additional safety factor to chlorpyrifos under the FQPA." These authors reviewed the language of the FQPA, the rationale for evaluation of chlorpyrifos because of its wide use and extensive database, the non-reproductive toxicity profile, the reproduction and developmental toxicity profiles, the rat developmental neurotoxicity study, and exposure from food, water and environment. Core studies reviewed included:

- Developmental toxicity studies in three species
- Two-generation reproduction studies in rats
- Three-generation reproduction study in rats with a teratology component
- Developmental neurotoxicity study in rats
- Several other relevant studies

The developmental neurotoxicity study in rats (Hoberman, 1999) was evaluated by Schardein and Scialli (1999). Females rats were exposed daily to chlorpyrifos from day 6 of gestation until day 10 of lactation. A large number of reproductive, maturational, reflex, and learning and memory tests were conducted on the offspring. High-dose dams (5 mg/kg/day) were clinically toxic, and newborn pups of these dams had a significant increase in mortality. Pup mortality coincided with maternal toxicity. Surviving high-dose pups had slower growth, and had brain weights that were proportional to their body size. Cognitive function was unaffected by treatment, even in the high-dose pups. The author (Hoberman, 1999) attributed these high-dose effects in pups to diminished maternal care due to maternal toxicity. Hoberman's conclusion about maternal toxicity was supported by Schardein and Scialli (1999). Low and mid-dose dams had no clinical effects, and pups from these dams grew normally.

The developmental neurotoxicity study conducted by Hoberman (1999) was accompanied by a companion study. The exposure pattern in the companion study (Mattsson et al., 1999) mimicked

the first study, but the purpose of the companion study was to measure plasma, RBC, and brain ChE activity of dams and fetuses (day 20) and pups (days 1, 5, 10, and later). In addition, analyses were conducted for chlorpyrifos, chlorpyrifos-oxon, and trichloropyridinol in blood of dams, fetuses, and nursing pups, and to analyze chlorpyrifos and chlorpyrifos-oxon in milk.

High-dose dams had very large decreases in plasma, RBC and brain ChE activity; gestation day 20 fetuses had very large decreases in plasma and RBC ChE, but had less brain ChE inhibition than their dams. Brain ChE activity of high-dose pups rapidly returned to control values while nursing. Dams at the low and mid-dose had inhibition of plasma and RBC ChE, and mid-dose dams also had slight inhibition of brain ChE. Fetuses and nursing pups of low and mid-dose dams had no inhibition of plasma, RBC or brain ChE. The NOEL in offspring for cholinesterase inhibition was 1 mg/kg/day maternal dose; there was no NOEL in dams as significant plasma and RBC AChE inhibition occurred at the lowest dose tested (0.3 mg/kg/day).

Chlorpyrifos was present in the milk, and an estimate of dosage to the high-dose pups was approximately 0.1 mg/kg/day from birth to 10 days of age. While nursing, plasma, RBC and brain ChE activity of high-dose pups returned to, or near to, control levels. Had the chlorpyrifos exposure level from milk been sufficient to cause ChE inhibition, one would expect a new plateau of inhibition and not a return of activity to control levels. This did not occur, and it was concluded that, at levels of exposure near the NOEL for adult rats (0.1 mg/kg/day), nursing pups did not demonstrate an increased level of sensitivity to chlorpyrifos exposure (Mattsson et al., 1999).

This body of evidence clearly shows a lack of increased sensitivity of the young to chlorpyrifos.

A.5. Acute and Chronic RfDs for Chlorpyrifos Should Remain Unchanged

A.5.1. Rationale

Chlorpyrifos RfDs are calculated from RBC AChE data from three scientifically-valid human volunteer studies (Coulston et al., 1972; Nolan et al., 1984; Kisicki et al., 1999).

To derive a conservative acute (single-dose) RfD, the NOEL for inhibition of RBC AChE was calculated from the Nolan et al. study, which evaluated RBC AChE inhibition in six male volunteers. The RBC-AChE NOEL was 0.5 mg/kg, the highest dose tested. In Kisicki et al., six men and six women were given single-oral doses of chlorpyrifos at 0.5, 1 or 2 mg/kg. No effects on RBC AChE were noted at 0.5 or 1 mg/kg. Consequently, the combined NOEL sample size from Nolan et al. and from Kisicki et al. was 18 males and 12 females.

A.5.2. Nolan et al. Study (1982, 1984) (MRID 00124144)

The objective of the Nolan et al. (1982, 1984) human study was to assess the kinetics of a single-oral dose of chlorpyrifos at 0.5 mg/kg, and a single dermal dose of chlorpyrifos at 5 mg/kg, in six healthy male volunteers. At the time this study was conducted, clinical studies were specifically excluded from GLP. However, review of the report did not provide any indication of unsatisfactory ethical or clinical practices.

No signs or symptoms of toxicity were observed. Plasma and erythrocyte cholinesterase activities were evaluated at 2, 6, 12 and 24 hours, then at multiple times over the next 29 days. Plasma ChE activity was promptly and significantly inhibited, but RBC AChE activity was not inhibited at any time point. Consequently, a NOEL for plasma ChE was not determined, and the NOEL for inhibition of RBC AChE was 0.5 mg/kg, the only dosage tested.

A.5.3. Kisicki et al. Study (1999)

A double-blind, randomized, placebo controlled human-exposure study was conducted by MDS Harris (Kisicki et al., 1999). Human volunteers were given higher doses in the Kisicki et al.

(1999) study than those in the Nolan et al. (1984) study. The primary objective of the Kisicki et al. (1999) human study was to assess the effects of chlorpyrifos on RBC AChE and to evaluate participants carefully for cholinergic symptoms and signs after a single oral dose of 0, 0.5, 1.0 or 2.0 mg/kg. This study was conducted according to GLP and GCP, and review of the report did not provide any indication of unsatisfactory ethical or clinical practices.

In Kisicki et al. (1999), six male and six female volunteers were randomly assigned to each dosage level, and chlorpyrifos was administered in a gelatin capsule. Blood samples were taken at –10, 0, 2, 4, 8, 12, 24, 36, 48, 72, 96, 120, 144, and 168 hours after treatment. Careful attention was paid to clinical signs and symptoms at numerous time points in the study. Hematology and clinical biochemistry investigations also were performed.

No treatment-related clinical effects were noted in any volunteer. No effects on RBC AChE were noted at any time at 0.5 or 1.0 mg/kg. At 2.0 mg/kg, one volunteer had an RBC AChE value that was more than 17% lower than her pre-exposure values, and this difference was attributed to treatment. There were no decreases in RBC AChE activity in the other 11 volunteers at 2.0 mg/kg. Consequently, the NOEL for RBC-AChE inhibition in this study was 1 mg/kg.

A.5.4. Calculation of the Acute RfD

The dose and endpoint for establishing the acute RfD was the 0.5 mg/kg/day NOEL based on the absence of RBC AChE inhibition in human volunteers in the Nolan et al. (1984) study and the Kisicki et al. (1999) study.

Uncertainty Factor (UF): 10 (10x for intraspecies variability, 1x for interspecies extrapolation and 1x for FQPA)

No interspecies UF is needed because the endpoint is from a human study. No FQPA factor is needed because appropriate animal studies indicate the fetus and neonate are not more sensitive to chlorpyrifos than the adult.

$$\text{Acute RfD} = \frac{\text{0.5 mg/kg/day (human NOEL)}}{\text{10 (intra-species UF)}} = 0.05 \text{ mg/kg/day}$$

A.5.5. Coulston et al. Study (1972) (MRID 00030754, 00043238)

The primary objective of the Coulston et al. (1972) human study was to assess the effects of chlorpyrifos on plasma ChE and RBC AChE after repeated oral doses of 0, 0.014, 0.03 or 0.1 mg/kg/day. This study was conducted before implementation of GLP. However, review of the report did not provide any indication of unsatisfactory ethical or clinical practices.

In Coulston et al. (1972), four male volunteers were randomly assigned to each dosage level, and chlorpyrifos was administered daily in a tablet. Blood samples were taken twice before treatment, and twice weekly after treatment began. Volunteers given 0.1 mg/kg/day were treated for nine days; those given 0.03 mg/kg/day were treated for 20 days, and those given 0.014 mg/kg/day were treated for 27 days. Urinalyses, hematology and clinical biochemistry investigations also were performed.

There was no inhibition of RBC AChE at any dosage level. Plasma ChE was not inhibited after three days, but was significantly inhibited after nine days at 0.1 mg/kg/day. Plasma ChE activity was slightly lower, but not statistically different, than controls at 0.03 mg/kg/day. No inhibition of plasma ChE or RBC AChE occurred at 0.014 mg/kg/day. Although one man complained of runny nose, blurred vision, and a feeling of faintness on day 9 of treatment at 0.1 mg/kg/day, the study physicians treated him for a cold and he was asymptomatic by the end of the day. The Coulston et al. (1972) study was reviewed recently by a panel of toxicology and medical experts (Clegg and van Gemert, 1999), who made the following conclusions about the symptomatic volunteer:

> "… To some degree, this diagnosis [a cold] is supported by the hematology, since lymphocyte counts were reduced and neutrophil counts were increased markedly, indicating a possible inflammatory reaction on day 8 of dosing, clearing by posttreatment d 5. In the absence of any indication of erythrocyte cholinesterase inhibition and with plasma cholinesterase inhibition being greater in two of the four

other individuals treated at the same dose level, these signs and symptoms are unlikely to have been induced by cholinesterase inhibition."

The NOEL for inhibition of RBC AChE was 0.1 mg/kg/day, the highest dose tested.

A.5.6. Calculation of the Chronic RfD

The dose and endpoint for establishing the chronic RfD was the 0.1 mg/kg/day NOEL based on the absence of RBC AChE inhibition in human volunteers in the Coulston et al. (1972).

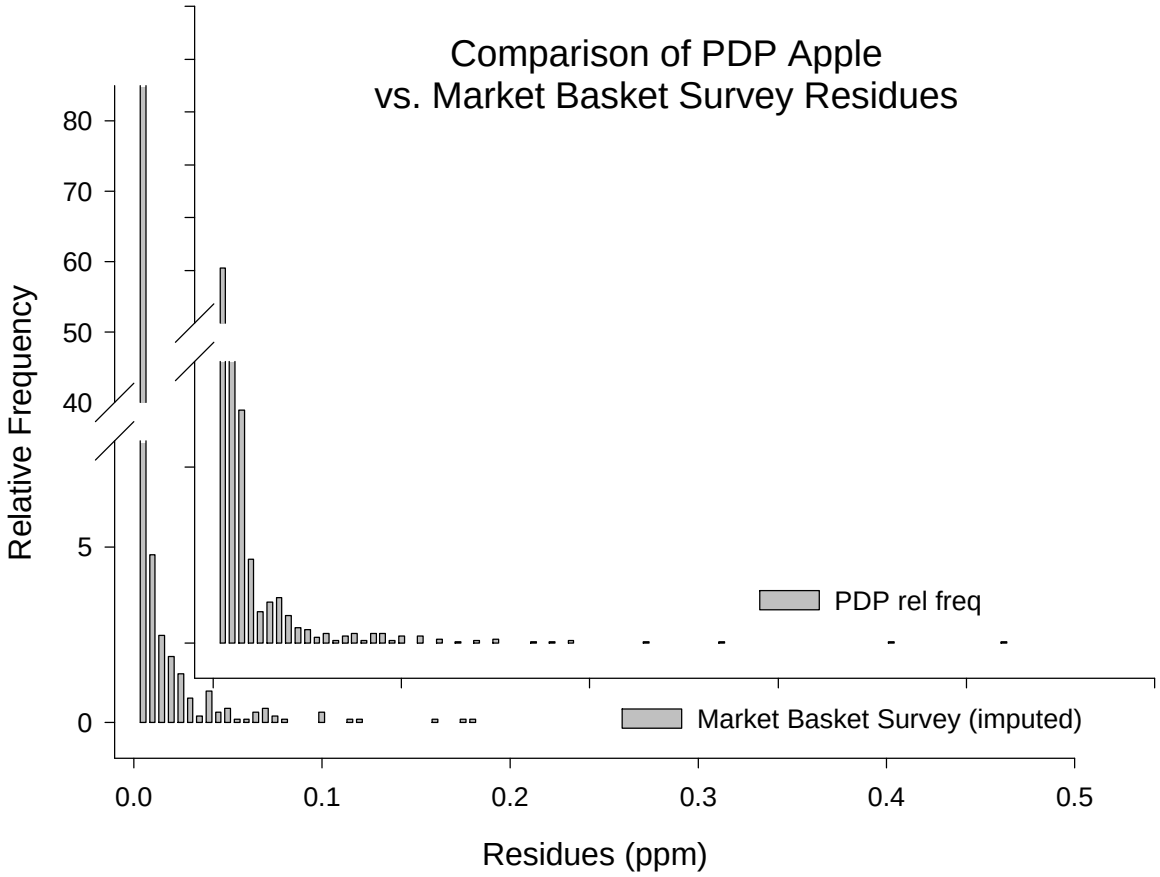
Uncertainty Factor (UF): 10 (10x for intraspecies variability, 1x for interspecies extrapolation and 1x for FQPA)

No interspecies UF is needed because the endpoint is from a human study. No FQPA factor is needed because appropriate animal studies indicate the fetus and neonate are not more sensitive to chlorpyrifos than the adult.

$$\text{Chronic RfD} = \frac{\text{0.1 mg/kg/day (human NOEL)}}{\text{10 (intra-species UF)}} = \text{0.01 mg/kg/day}$$

Appendix B: DAS Acute Dietary Risk Assessment

B.1. Graph Comparing PDP Apple Data to Marketbasket Data



B.2. EPA Baseline Acute Dietary Assessment without Cranberries

Dow AgroSciences Ver. 6.79
DEEM ACUTE analysis for CHLORPYRIFOS (1989-92 data)
Residue file: 059101r(RMBcr).R96 Adjustment factor #2 NOT used.
Analysis Date: 08-11-1999/13:47:48 Residue file dated: 08-10-1999/07:41:17/7
Acute Reference Dose (aRfD) = 0.001700 mg/kg body-wt/day
MC iterations = 1000 MC list in residue file MC seed = 10
Run Comment: EPA analysis; de-composited PDP/FDA (FT); no cranberries
==========

Summary calculations:

	95th Percentile		99th Percentile		99.9th Percentile	
	Exposure	% aRfD	Exposure	% aRfD	Exposure	% aRfD
U.S. pop - all seasons:	0.000066	3.90	0.000127	7.48	0.000385	22.64
All infants (<1 year):	0.000121	7.10	0.000237	13.93	0.000739	43.49
Nursing infants (<1 year):	0.000048	2.85	0.000160	9.39	0.000715	42.08
Non-nursing infants (<1 yr):	0.000137	8.05	0.000258	15.18	0.000730	42.96
Children (1-6 years):	0.000123	7.26	0.000227	13.36	0.000751	44.18
Children (7-12 years):	0.000080	4.72	0.000159	9.35	0.000541	31.82
Females (13+/nursing):	0.000055	3.21	0.000115	6.75	0.000420	24.68

B.3. Revised Acute Dietary Assessment

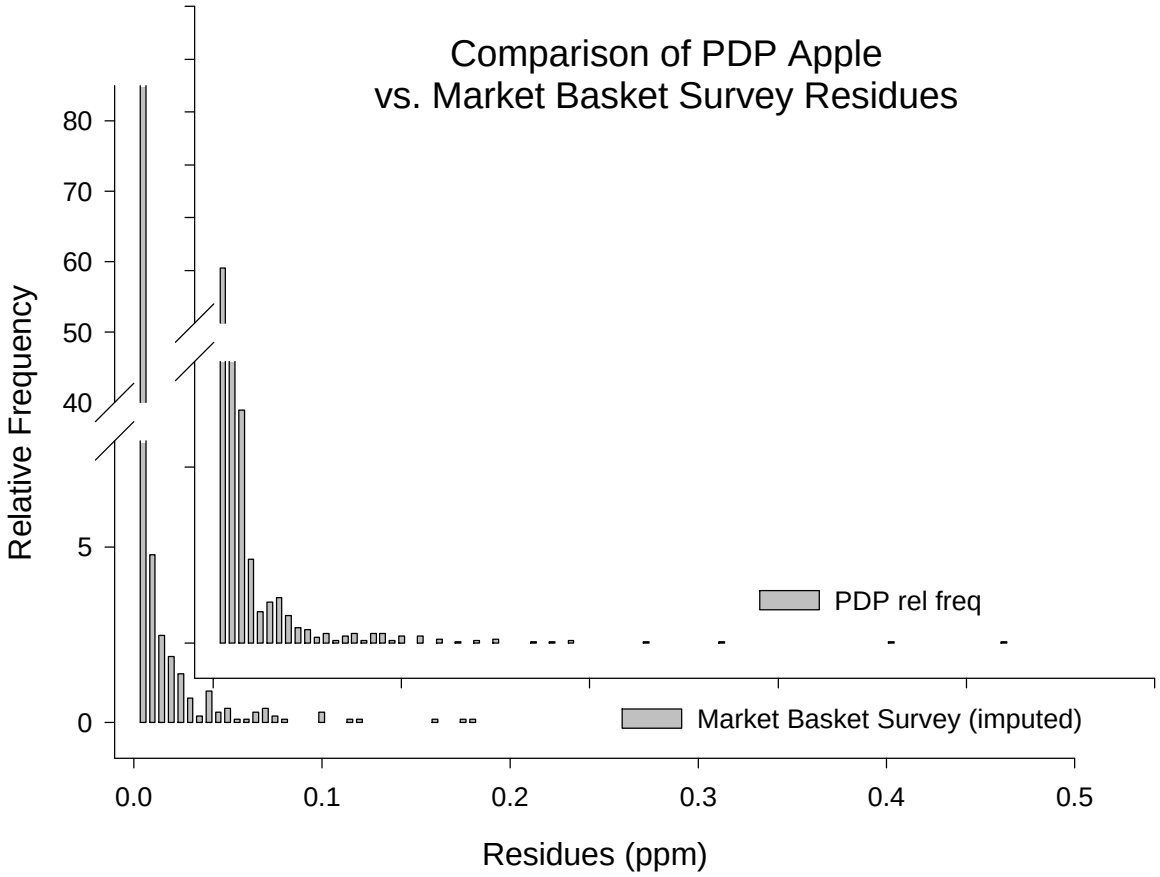
Dow AgroSciences Ver. 6.79
DEEM ACUTE analysis for CHLORPYRIFOS (1989-92 data)
Residue file: 059101r(crpopgarbee).R96 Adjustment factor #2 NOT used.
Analysis Date: 08-26-1999/20:11:25 Residue file dated: 08-26-1999/14:06:43/7
Acute Reference Dose (aRfD) = 0.001700 mg/kg body-wt/day
MC iterations = 1200 MC list in residue file MC seed = 10
Run Comment: EPA analysis; de-composited PDP/FDA (FT)
==========

Summary calculations:

	95th Percentile		99th Percentile		99.9th Percentile	
	Exposure	% aRfD	Exposure	% aRfD	Exposure	% aRfD
U.S. pop - all seasons:	0.000066	3.90	0.000127	7.49	0.000386	22.71
All infants (<1 year):	0.000121	7.13	0.000239	14.05	0.000757	44.50
Nursing infants (<1 year):	0.000048	2.85	0.000163	9.58	0.000839	49.36
Non-nursing infants (<1 yr):	0.000137	8.07	0.000258	15.17	0.000723	42.52
Children (1-6 years):	0.000124	7.27	0.000227	13.34	0.000754	44.34
Children (7-12 years):	0.000080	4.71	0.000158	9.30	0.000537	31.58
Females (13+/nursing):	0.000054	3.20	0.000115	6.78	0.000430	25.28

Appendix C: DAS Chronic Non-Cancer Dietary Exposure Assessment

C.1. Graph Comparing PDP and Marketbasket Data Submitted by DAS



C.2. Risk Assessment Using Reference Dose Proposed by DAS

Dow AgroSciences Ver. 6.76
DEEM Chronic analysis for CHLORPYRIFOS (1989-92 data)
Residue file name: C:\ched\Chlonionmilkwatersybnnopop(revm).R96
Adjustment factor #2 NOT used.
Analysis Date 08-26-1999/11:52:59 Residue file dated: 08-26-1999/11:50:15/7
Reference dose (RfD, CHRONIC) = .01 mg/kg bw/day
COMMENT 1: DAS Chronic RfD: 0.01 Revised: No beets

Total exposure by population subgroup

Population Subgroup	Total Exposure mg/kg body wt/day	Percent of Rfd
U.S. Population (total)	0.000017	0.2%
U.S. Population (spring season)	0.000015	0.1%
U.S. Population (summer season)	0.000017	0.2%
U.S. Population (autumn season)	0.000017	0.2%
U.S. Population (winter season)	0.000017	0.2%
Northeast region	0.000017	0.2%
Midwest region	0.000016	0.2%
Southern region	0.000016	0.2%
Western region	0.000018	0.2%
Hispanics	0.000016	0.2%
Non-hispanic whites	0.000017	0.2%
Non-hispanic blacks	0.000014	0.1%
Non-hisp/non-white/non-black)	0.000017	0.2%
All infants (< 1 year)	0.000016	0.2%
Nursing infants	0.000010	0.1%
Non-nursing infants	0.000019	0.2%
Children 1-6 yrs	0.000041	0.4%
Children 7-12 yrs	0.000026	0.3%
Females 13-19(not preg or nursing)	0.000012	0.1%
Females 20+ (not preg or nursing)	0.000012	0.1%
Females 13-50 yrs	0.000012	0.1%

Females 13+ (preg/not nursing)	0.000014	0.1%
Females 13+ (nursing)	0.000020	0.2%
Males 13-19 yrs	0.000015	0.2%
Males 20+ yrs	0.000012	0.1%
Seniors 55+	0.000012	0.1%
Pacific Region	0.000019	0.2%

C.3. Risk Assessment Using Reference Dose Proposed by EPA

Dow AgroSciences Ver. 6.76
DEEM Chronic analysis for CHLORPYRIFOS (1989-92 data)
Residue file name: C:\ched\Chlonionmilkwatersybnnopop(revm).R96
Adjustment factor #2 NOT used.
Analysis Date 08-26-1999/11:53:43 Residue file dated: 08-26-1999/11:50:15/7
Reference dose (RfD, CHRONIC) = .0001 mg/kg bw/day
COMMENT 1: EPA Chronic RfD: 0.01 Revised: No beets

Total exposure by population subgroup

Population Subgroup	Total Exposure mg/kg body wt/day	Percent of Rfd
U.S. Population (total)	0.000017	16.5%
U.S. Population (spring season)	0.000015	14.9%
U.S. Population (summer season)	0.000017	16.5%
U.S. Population (autumn season)	0.000017	17.5%
U.S. Population (winter season)	0.000017	17.1%
Northeast region	0.000017	16.5%
Midwest region	0.000016	16.5%
Southern region	0.000016	15.6%
Western region	0.000018	18.1%
Hispanics	0.000016	16.0%
Non-hispanic whites	0.000017	17.0%
Non-hispanic blacks	0.000014	13.7%
Non-hisp/non-white/non-black)	0.000017	17.4%
All infants (< 1 year)	0.000016	16.3%
Nursing infants	0.000010	9.6%
Non-nursing infants	0.000019	19.1%
Children 1-6 yrs	0.000041	41.4%
Children 7-12 yrs	0.000026	26.4%
Females 13-19(not preg or nursing)	0.000012	12.3%
Females 20+ (not preg or nursing)	0.000012	12.1%
Females 13-50 yrs	0.000012	12.4%

Females 13+ (preg/not nursing)	0.000014	13.9%
Females 13+ (nursing)	0.000020	20.3%
Males 13-19 yrs	0.000015	15.1%
Males 20+ yrs	0.000012	12.3%
Seniors 55+	0.000012	12.1%
Pacific Region	0.000019	18.6%

C.4. Revised Residue Data File

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"Chlorpyrifos"
 0.0003
NEWN,          0.005
NOEL,          0.03          0.5           0
08-26-1999/11:50:15
-1  "This is for chronic dietary exposure analysis.  Revised:  No beets. "
 999
 8    01010AA,O,   0.1       1          1         0   "Cranberries", "Field trial data"
 9    01010JA,O,   0.1       0.3        1         0   "Cranberries-juice", "Field trial data Grape processing factor"
 13   01014AA,O,   0.00286   1          1         4   "Grapes", "PDP 1994-1997"
    11       Uncooked,             0.00286        1          1         "PDP 1994-1997"
    12       Cooked: NFS,          0.00286        1          1         "PDP 1994-1997"
    31       Canned: NFS,          0.00286        1          1         "PDP 1994-1997"
    41       Frozen: NFS,          0.00286        1          1         "PDP 1994-1997"
 14   01014DA,O,   0.00286   0.17       1         6   "Grapes-raisins", "PDP 1994-1997"
    11       Uncooked,             0.00286        0.17       1         "PDP 1994-1997"
    12       Cooked: NFS,          0.00286        0.17       1         "PDP 1994-1997"
    13       Baked,                0.00286        0.17       1         "PDP 1994-1997"
    14       Boiled,               0.00286        0.17       1         "PDP 1994-1997"
    18       Dried,                0.00286        0.17       1         "PDP 1994-1997"
    42       Frozen: Cooked,       0.00286        0.17       1         "PDP 1994-1997"
 15   01014JA,O,   0.00286   0.3        1         6   "Grapes-juice", "PDP 1994-1997"
    11       Uncooked,             0.00286        0.3        1         "PDP 1994-1997"
    12       Cooked: NFS,          0.00286        0.3        1         "PDP 1994-1997"
    14       Boiled,               0.00286        0.3        1         "PDP 1994-1997"
    31       Canned: NFS,          0.00286        0.3        1         "PDP 1994-1997"
    34       Canned: Boiled,       0.00286        0.3        1         "PDP 1994-1997"
    41       Frozen: NFS,          0.00286        0.3        1         "PDP 1994-1997"
 17   01016AA,O,   0.00022   1          1         0   "Strawberries", "FDA data"
 20   02001AA,10,  0.000914  1          1         0   "Citrus citron", "PDP translated from oranges"
 22   02002AB,10,  0.000914  1          1         0   "Grapefruit-peeled fruit", "Translated from oranges"
 23   02002JA,10,  0.001     1          1         0   "Grapefruit-juice", "MBS orange juice 10% CT"
 24   02003AA,10,  0.000914  1          1         0   "Kumquats", "Translated from oranges"
 26   02004AB,10,  0.000914  1          1         0   "Lemons-peeled fruit", "PDP from orange juice"
 27   02004HA,10,  0.000914  1          1         0   "Lemons-peel", "PDP from orange juice"
 28   02004JA,10,  0.001     2          1         0   "Lemons-juice", "MBS orange juice 10% CT"
 30   02005AB,10,  0.000914  1          1         0   "Limes-peeled fruit", "PDP from oranges"
 31   02005HA,10,  0.000914  1          1         0   "Limes-peel", "PDP from oranges"
 32   02005JA,10,  0.001     2          1         0   "Limes-juice", "MBS orange juice 10% CT"
 33   02006JC,10,  0.001     3          1         0   "Oranges-juice-concentrate", "MBS orange juice with 10% CT"
 34   02006AB,10,  0.000914  1          1         0   "Oranges-peeled fruit", "PDP"
 35   02006HA,10,  0.000914  1          1         0   "Oranges-peel", "PDP"
 36   02006JA,10,  0.001     1          1         0   "Oranges-juice", "MBS orange juice with 10% CT"
 37   02007AA,10,  0.000914  1          1         0   "Tangelos", "PDP from Oranges"
 38   02008AA,10,  0.000914  1          1         0   "Tangerines", "PDP from Oranges"
 39   02008JA,10,  0.001     1          1         0   "Tangerines-juice", "MBS orange juice 10% CT"
 40   03001AA,14,  0.014     1          1         0   "Almonds", "Field trials from Walnuts and Almonds"
 41   03002AA,14,  0.0045    1          1         0   "Brazil nuts", "Field trials from Walnuts and Almonds"
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42 03003AA,14, 0.0045 1 1 0 "Cashews", "Field trials from Walnuts and Almonds"
43 03004AA,14, 0.0045 1 1 0 "Chestnuts", "Field trials from Walnuts and Almonds"
44 03005AA,14, 0.0045 1 1 0 "Filberts (hazelnuts)", "Field trials from Walnuts and Almonds"
45 03006AA,14, 0.0045 1 1 0 "Hickory nuts", "Field trials from Walnuts and Almonds"
46 03007AA,14, 0.0045 1 1 0 "Macadamia nuts (bush nuts)", "Field trials from Walnuts and Almonds"
47 03008AA,14, 0.018 1 1 0 "Pecans", "Field trials from Walnuts and Almonds"
48 03009AA,14, 0.02 1 1 0 "Walnuts", "Field trials from Walnuts and Almonds"
49 03010AA,14, 0.0045 1 1 0 "Butter nuts", "Field trials from Walnuts and Almonds"
51 03013AA,14, 0.0045 1 1 0 "Beech-nuts", "Field trials from Walnuts and Almonds"
52 04001AA,11, 0.0048 1 1 11 "Apples", "Market basket with 53% crop treated"
11 Uncooked, 0.0048 1 1 "Market basket with 53% crop treated"
12 Cooked: NFS, 0.0048 1 1 "Market basket with 53% crop treated"
13 Baked, 0.001 1 1 "Market basket with applesauce"
14 Boiled, 0.001 1 1 "Market basket with applesauce"
15 Fried, 0.001 1 1 "Market basket with applesauce"
18 Dried, 0.0048 1 1 "Market basket with 53% crop treated"
31 Canned: NFS, 0.001 1 1 "Market basket for applesauce with 53% crop treated"
32 Canned: Cooked, 0.001 1 1 "Market basket for applesauce with 53% crop treated"
33 Canned: Baked, 0.001 1 1 "Market basket for applesauce with 53% crop treated"
34 Canned: Boiled, 0.001 1 1 "Market basket for applesauce with 53% crop treated"
42 Frozen: Cooked, 0.001 1 1 "Market basket for applesauce with 53% crop treated"
53 04001DA,11, 0.0076 8 1 4 "Apples-dried", "PDP 94-96 with 53% crop treated"
13 Baked, 0.0076 8 1 "PDP 94-96 with 53% crop treated"
14 Boiled, 0.0076 8 1 "PDP 94-96 with 53% crop treated"
18 Dried, 0.0076 8 1 "PDP 94-96 with 53% crop treated"
42 Frozen: Cooked, 0.0076 8 1 "PDP 94-96 with 53% crop treated"
54 04001JA,11, 0.0004 1 1 5 "Apples-juice/cider", "MBS apple juice with 53% CT"
11 Uncooked, 0.0004 1 1 "MBS apple juice with 53% CT"
12 Cooked: NFS, 0.0004 1 1 "MBS apple juice with 53% CT"
14 Boiled, 0.0004 1 1 "MBS apple juice with 53% CT"
31 Canned: NFS, 0.0004 1 1 "MBS apple juice with 53% CT"
41 Frozen: NFS, 0.0004 1 1 "MBS apple juice with 53% CT"
56 04003AA,11, 0.0007 1 1 5 "Pears", "1997 PDP"
11 Uncooked, 0.0007 1 1 "1997 PDP"
12 Cooked: NFS, 0.0007 1 1 "1997 PDP"
13 Baked, 0.0007 1 1 "1997 PDP"
14 Boiled, 0.0007 1 1 "1997 PDP"
31 Canned: NFS, 0.0007 1 1 "1997 PDP"
57 04003DA,11, 0.000965 6.25 1 3 "Pears-dried", "1997 PDP"
13 Baked, 0.000965 6.25 1 "1997 PDP"
14 Boiled, 0.000965 6.25 1 "1997 PDP"
18 Dried, 0.000965 6.25 1 "1997 PDP"
61 05002AA,12, 0.0012 1 1 0 "Cherries", "FDA"
62 05002DA,12, 0.0012 4 1 0 "Cherries-dried", "FDA"
63 05002JA,12, 0.0012 0.3 1 4 "Cherries-juice", "FDA"
13 Baked, 0.0012 0.3 1 "FDA"
14 Boiled, 0.0012 0.3 1 "FDA"
31 Canned: NFS, 0.0012 0.3 1 "FDA"
41 Frozen: NFS, 0.0012 0.3 1 "FDA"
64 05003AA,12, 0.000388 1 1 1 "Nectarines", "PDP Peaches"
11 Uncooked, 0.000388 1 1 "PDP Peaches"

65 05004AA,12, 0.000388 1 1 6 "Peaches", "PDP"
11 Uncooked, 0.000388 1 1 "PDP"
12 Cooked: NFS, 0.000388 1 1 "PDP"
13 Baked, 0.000388 1 1 "PDP"
14 Boiled, 0.000388 1 1 "PDP"
31 Canned: NFS, 0.000425 1 1 "PDP 1997 canned"
41 Frozen: NFS, 0.000388 1 1 "PDP"
66 05004DA,12, 0.000388 7 1 0 "Peaches-dried", "PDP"
67 05005AA,12, 0.000388 1 1 0 "Plums (damsons)", "PDP from peaches"
68 05005DA,12, 0.000388 5 1 0 "Plums-prunes (dried)", "PDP from peaches"
69 05005JA,12, 0.000388 1.4 1 0 "Plums/prune-juice", "PDP from peaches"
72 06002AB,O, 0.000424 1 1 0 "Bananas", "PDP 94 96"
73 06002DA,O, 0.000424 3.9 1 0 "Bananas-dried", "PDP 94 96"
78 06005AA,O, 0.0001 1 1 0 "Figs", "tolerance and 1% crop treated"
94 06016AA,O, 0.000424 1 1 0 "Plantains-ripe", "PDP 94 and 95"
97 06018AA,O, 0.00005 1 1 0 "Kiwi fruit", "FDA"
148 10010AA,9B, 0.000198 1 1 0 "Cucumbers", "FDA data"
149 10011AA,9B, 0.000198 1 1 0 "Pumpkin", "Translated from Cucumbers"
155 11003AA,8, 0.0083 1 1 0 "Peppers-sweet(garden)", "FDA "
156 11003AB,8, 0.0083 1 1 0 "Peppers-chilli incl jalapeno", "FDA "
157 11003AD,8, 0.0083 1 1 0 "Peppers-other", "FDA "
159 11005AA,8, 0.0044 1 1 0 "Tomatoes-whole", "PDP"
160 11005JA,8, 0.0044 0.3 1 0 "Tomatoes-juice", "PDP and processing study"
161 11005RA,8, 0.0044 0.1 1 0 "Tomatoes-puree", "PDP and processing study"
162 11005TA,8, 0.0044 0.1 1 0 "Tomatoes-paste", "PDP and processing study"
163 11005UA,8, 0.0044 0.1 1 0 "Tomatoes-catsup", "PDP and processing study"
168 13005AA,5A, 0.001486 1 1 0 "Broccoli", "PDP 94"
169 13006AA,5A, 0.001486 1 1 0 "Brussels sprouts", "PDP 94 from broccoli"
170 13007AA,5A, 0.00111 1 1 0 "Cabbage-green and red", "FDA data"
171 13008AA,5A, 0.000053 1 1 0 "Cauliflower", "FDA"
172 13009AA,5B, 0.0015 1 1 0 "Collards", "FDA"
174 13011AA,5B, 0.006 1 1 0 "Kale", "FDA"
175 13012AA,5A, 0.0015 1 1 0 "Kohlrabi", "collards"
183 13021AA,5B, 0.0015 1 1 0 "Mustard greens", "collards"
187 13025AA,4B, 0.006 1 1 0 "Swiss chard", "from Kale FDA"
188 13026AA,2, 0.001211 1 1 0 "Turnips-tops", "Sweet Potato data"
195 13049AA,O, 0.00286 1.5 1 1 "Grapes-leaves", "PDP 1994-1997"
14 Boiled, 0.00286 1.5 1 "PDP 1994-1997"
205 14011AA,3, 0.00003 1 1 0 "Onions-dry-bulb (cipollini)", "1992 - 1997 FDA and 19% crop treated"
212 14014AA,1AB, 0.00034 1 1 0 "Radishes-roots", "FDA"
213 14014AB,2, 0.00034 1 1 0 "Radishes-tops", "FDA"
214 14015AA,1AB, 0.001211 1 1 0 "Rutabagas-roots", "PDP from sweet potato"
215 14015AB,2, 0.001211 1 1 0 "Rutabagas-tops", "PDP from sweet potato"
218 14018AA,1CD, 0.001211 1 1 6 "Sweet potatoes (incl yams)", "PDP 1994-1997"
12 Cooked: NFS, 0.001211 1 1 "PDP 1994-1997"
13 Baked, 0.001211 1 1 "PDP 1994-1997"
14 Boiled, 0.001211 1 1 "PDP 1994-1997"
15 Fried, 0.001211 1 1 "PDP 1994-1997"
32 Canned: Cooked, 0.001211 1 1 "PDP 1994-1997"
34 Canned: Boiled, 0.001211 1 1 "PDP 1994-1997"
219 14019AA,1AB, 0.001211 1 1 0 "Turnips-roots", "Sweet Potato data"

227 15001AA,6C, 0.00025 1 1 0 "Beans-dry-great northern", "Tolerance and % crop treated"
228 15001AB,6C, 0.00025 1 1 0 "Beans-dry-kidney", "Tolerance and % crop treated"
229 15001AC,6C, 0.00025 1 1 0 "Beans-dry-lima", "Tolerance and % crop treated"
230 15001AD,6C, 0.00025 1 1 0 "Beans-dry-navy (pea)", "Tolerance and % crop treated"
231 15001AE,6C, 0.00025 1 1 0 "Beans-dry-other", "Tolerance and % crop treated"
232 15001AF,6C, 0.00025 1 1 0 "Beans-dry-pinto", "Tolerance and % crop treated"
233 15002AA,6B, 0.00005 1 1 0 "Beans-succulent-lima", "PDP and % crop treated"
234 15003AA,6A, 0.000032 1 1 0 "Beans-succulent-green", "PDP 96 and 97"
235 15003AB,6A, 0.0005 1 1 0 "Beans-succulent-other", "Tolerance and % crop treated"
236 15003AC,6A, 0.0005 1 1 0 "Beans-succulent-yellow/wax", "Tolerance and % crop treated"
238 15005AA,15, 0.00033 1 1 8 "Corn/sweet", "FDA"
11 Uncooked, 0.00033 1 1 "FDA"
12 Cooked: NFS, 0.00022 1 1 "PDP"
13 Baked, 0.00022 1 1 "PDP"
14 Boiled, 0.00022 1 1 "PDP"
32 Canned: Cooked, 0.00022 1 1 "PDP"
34 Canned: Boiled, 0.00022 1 1 "PDP"
35 Canned: Fried, 0.00022 1 1 "PDP"
42 Frozen: Cooked, 0.00022 1 1 "PDP"
240 15007AA,6C, 0.0005 1 1 0 "Peas (garden)-dry", "Tolerance and % crop treated"
241 15009AA,6AB, 0.000033 1 1 0 "Peas (garden)-green", "PDP 1996"
243 15011AB,6C, 0.00025 1 1 0 "Lentils", "Tolerance and % crop treated"
244 15013AA,6C, 0.00025 1 1 0 "Mung beans (sprouts)", "from beans"
249 15022AA,6C, 0.00025 1 1 0 "Beans-dry-broadbeans", "Tolerance and % crop treated"
250 15022AB,6B, 0.00005 1 1 0 "Beans-succulent-broadbeans", "PDP and % crop treated"
251 15023AA,6C, 0.00025 1 1 0 "Beans-dry-pigeon beans", "Tolerance and % crop treated"
253 15027AA,6, 0.0005 1 1 0 "Beans-unspecified", "Tolerance and % crop treated"
255 15029AA,6A, 0.00032 0.33 1 0 "Soybeans-sprouted seeds", "Knizner Memo."
256 15030AA,6C, 0.00025 1 1 0 "Beans-dry-hyacinth", "Tolerance and % crop treated"
257 15030AB,6, 0.0005 1 1 0 "Beans-succulent-hyacinth", "Tolerance and % crop treated"
258 15031AA,6C, 0.00025 1 1 0 "Beans-dry-blackeye peas/cowpea", "Tolerance and % crop treated"
259 15032AA,6C, 0.00025 1 1 0 "Beans-dry-garbanzo/chick pea", "Tolerance and % crop treated"
260 16002AA,O, 0.0006 1 1 0 "Asparagus", "92-97 FDA and % crop treated"
261 16003AA,O, 0.001 1 1 0 "Mushrooms", "tolerance and percent crop treated"
266 24002EA,15, 0.00088 1 1 0 "Corn grain-endosperm", "Field trial"
267 24002HA,15, 0.00088 1 1 0 "Corn grain-bran", "Field trial"
268 24002SA,15, 0.00088 1.5 1 0 "Corn grain/sugar/hfcs", "Field trial"
272 24005AA,15, 0.000747 1 1 0 "Rye-rough", "PDP from wheat"
273 24005GA,15, 0.000747 1 1 0 "Rye-germ", "PDP from wheat"
274 24005WA,15, 0.000747 1 1 0 "Rye-flour", "PDP from wheat"
276 24007AA,15, 0.0032 1 1 0 "Wheat-rough", "PDP 1995-1997"
277 24007GA,15, 0.0032 1 1 0 "Wheat-germ", "PDP 1995-1997"
278 24007HA,15, 0.0032 1 1 0 "Wheat-bran", "PDP 1995-1997"
279 24007WA,15, 0.0032 0.145 1 0 "Wheat-flour", "PDP 1995-1997"
282 25002SA,1A, 0.001211 1 1 1 "Sugar-beet", "PDP from Sweet Potato"
98 Refined, 0.001211 0.005 1 "PDP from Sweet Potato"
283 25003SA,O, 0.01 1 1 1 "Sugar-cane", "Tolerance"
98 Refined, 0.01 0.005 1 "tolerance"
284 25003SB,O, 0.01 1 1 1 "Sugar-cane/molasses", "tolerance"
13 Baked, 0.01 1 1 "tolerance"
286 26001AA,15, 0.0011 1 1 0 "Buckwheat", "PDP"

287 26011AA,6C, 0.00025 1 1 0 "Guar beans", "Tolerance and % crop treated"
289 27002OA,15, 0.00088 4.5 1 0 "Corn grain-oil", "Field trial"
290 27003OA,O, 0.0027 1 1 0 "Cottonseed-oil", "Field trial % crop treated and processing factor."
293 27007OA,O, 0.000022 2 1 0 "Peanuts-oil", "steve knizner 7/95 ar memo for the processing fact"
297 27010OA,6A, 0.00032 0.14 1 0 "Soybeans-oil", "Knizner Memo. Reduction factor."
298 27011OA,O, 0.00046 1 1 0 "Sunflower-oil", "knizner 7/95 memo"
303 15023AA,6A, 0.00032 1 1 0 "Soybean-other", "Knizner Memo."
304 28023AB,6A, 0.00032 1 1 0 "Soybeans-mature seeds dry", "Knizner Memo."
305 28023WA,6A, 0.00032 1 1 0 "Soybeans-flour (full fat)", "Knizner Memo."
306 28023WB,6A, 0.00032 1 1 0 "Soybeans-flour (low fat)", "Knizner Memo."
307 28023WC,6A, 0.00032 1 1 0 "Soybeans-flour (defatted)", "Knizner Memo."
311 28080OA,O, 2.16 1 1 0 "Peppermint-oil", "Tolerance of Hay, 10x CF, percent crop treated"
313 28081OA,O, 2.16 1 1 0 "Spearmint-oil", "Hay tolerance x 10 CF x percent crop treated"
315 43058AA,O, 0.00286 1 1 1 "Grapes-wine and sherry", "PDP 1994-1997"
99 Alcohol/Fermented/Di, 0.00286 1 1 "PDP 1994-1997"
318 50000DB,D, 0.00023 1 1 0 "Milk-nonfat solids", "Market basket"
319 50000FA,D, 0.00023 1 1 0 "Milk-fat solids", "Market basket"
320 50000SA,D, 0.00023 1 1 0 "Milk sugar (lactose)", "Market basket"
321 53001BA,M, 0.00101 1 1 0 "Beef-meat byproducts", "Registrants' Market Basket Survey"
322 53001BB,M, 0.00101 1 1 0 "Beef-other organ meats", "Registrants' Market Basket Survey"
323 53001DA,M, 0.00101 1.92 1 0 "Beef-dried", "Registrants' Market Basket Survey"
324 53001FA,M, 0.00504 1 1 0 "Beef-fat w/o bones", "Registrants' Market Basket Survey"
325 53001KA,M, 0.00101 1 1 0 "Beef-kidney", "Registrants' Market Basket Survey"
326 53001LA,M, 0.00101 1 1 0 "Beef-liver", "Registrants' Market Basket Survey"
327 53001MA,M, 0.00101 1 1 0 "Beef-lean (fat/free) w/o bones", "Registrants' Market Basket Survey"
328 53002BA,M, 0.00101 1 1 0 "Goat-meat byproducts", "Registrants' Market Basket Survey"
329 53002BB,M, 0.00101 1 1 0 "Goat-other organ meats", "Registrants' Market Basket Survey"
330 53002FA,M, 0.00504 1 1 0 "Goat-fat w/o bone", "Registrants' Market Basket Survey"
331 53002KA,M, 0.00101 1 1 0 "Goat-kidney", "Registrants' Market Basket Survey"
332 53002LA,M, 0.00101 1 1 0 "Goat-liver", "Registrants' Market Basket Survey"
333 53002MA,M, 0.00101 1 1 0 "Goat-lean (fat/free) w/o bone", "Registrants' Market Basket Survey"
334 53003AA,M, 0.00101 1 1 0 "Horsemeat", "Translated from Beef."
336 53005BA,M, 0.001 1 1 0 "Sheep-meat byproducts", "Market Basket"
337 53005BB,M, 0.001 1 1 0 "Sheep-other organ meats", "Market Basket"
338 53005FA,M, 0.005 1 1 0 "Sheep-fat w/o bone", "Market Basket"
339 53005KA,M, 0.001 1 1 0 "Sheep-kidney", "Market Basket"
340 53005LA,M, 0.001 1 1 0 "Sheep-liver", "Market Basket"
341 53005MA,M, 0.001 1 1 0 "Sheep-lean (fat free) w/o bone", "Market Basket"
342 53006BA,M, 0.00101 1 1 0 "Pork-meat byproducts", "Pork Sausage"
343 53006BB,M, 0.00101 1 1 0 "Pork-other organ meats", "Pork Sausage"
344 53006FA,M, 0.00404 1 1 0 "Pork-fat w/o bone", "Pork Sausage"
345 53006KA,M, 0.00101 1 1 0 "Pork-kidney", "Pork Sausage"
346 53006LA,M, 0.00101 1 1 0 "Pork-liver", "Pork Sausage"
347 53006MA,M, 0.00101 1 1 0 "Pork-lean (fat free) w/o bone", "Pork Sausage"
355 55008BA,P, 0.000001 1 1 0 "Turkey-byproducts", "Dietary Burden Calculation"
356 55008LA,P, 0.000001 1 1 0 "Turkey-giblets (liver)", "Dietary Burden Calculation"
357 55008MA,P, 0.000013 1 1 0 "Turkey--fat w/o bones", "Dietary Burden Calculation"
358 55008MB,P, 0.000001 1 1 0 "Turkey- lean/fat free w/o bones", "Dietary Burden Calculation"

360 55013BA,P, 0.000001 1 1 0 "Poultry-other-lean (fat free) w/o bone", "dietary burden"
361 55013LA,P, 0.000001 1 1 0 "Poultry-other-giblets(liver)", "dietary burden"
362 55013MA,P, 0.000013 1 1 0 "Poultry-other-fat w/o bones", "dietary burden"
363 55014AA,P, 0.000002 1 1 0 "Eggs-whole", "Dietary Burden"
364 55014AB,P, 0.000002 1 1 0 "Eggs-white only", "Dietary Burden"
365 55014AC,P, 0.000002 1 1 0 "Eggs-yolk only", "Dietary Burden"
366 55015BA,P, 0.000001 1 1 0 "Chicken-byproducts", "Dietary Burden Calculations"
367 55015LA,P, 0.000001 1 1 0 "Chicken-giblets(liver)", "Dietary Burden Calculations"
368 55015MA,P, 0.000013 1 1 0 "Chicken-fat w/o bones", "Dietary Burden Calculations"
369 55015MB,P, 0.000001 1 1 0 "Chicken-lean/fat free w/o bones", "Dietary Burden Calculations"
377 04001JC,11, 0.0004 3 1 4 "Apples-juice-concentrate", "MBS apple juice with 53% CT"
12 Cooked: NFS, 0.0004 3 1 "MBS apple juice with 53% CT"
13 Baked, 0.0004 3 1 "MBS apple juice with 53% CT"
31 Canned: NFS, 0.0004 3 1 "MBS apple juice with 53% CT"
41 Frozen: NFS, 0.0004 3 1 "MBS apple juice with 53% CT"
378 06002NA,O, 0.000424 1 1 0 "Bananas-juice", "PDP 94 96"
379 25002MO,1A, 0.001211 1 1 1 "Sugar-beet-molasses", "PDP from Sweet Potato"
98 Refined, 0.001211 0.005 1 "PDP from Sweet Potato "
383 13007SA,5B, 0.00111 1 1 0 "Cabbage-savoy", "FDA data"
385 55015EL,P, 0.000001 1 1 0 "Chicken-giblets (excl. liver)", "Dietary Burden Calculations"
388 24002MO,15, 0.00088 0.05 1 0 "Corn grain/sugar-molasses", "Field trial"
389 01010JC,O, 0.1 1 1 0 "Cranberries-juice-concentrate", "Field trial data Grape processing factor"
392 01014JC,O, 0.00286 1 1 5 "Grapes-juice-concentrate", "PDP 1994-1997"
12 Cooked: NFS, 0.00286 1 1 "PDP 1994-1997"
13 Baked, 0.00286 1 1 "PDP 1994-1997"
14 Boiled, 0.00286 1 1 "PDP 1994-1997"
31 Canned: NFS, 0.00286 1 1 "PDP 1994-1997"
41 Frozen: NFS, 0.00286 1 1 "PDP 1994-1997"
402 05004JA,12, 0.000388 1 1 2 "Peaches-juice", "PDP"
11 Uncooked, 0.000388 1 1 "PDP"
31 Canned: NFS, 0.000425 1 1 "PDP 1997 canned data"
403 15006BT,O, 0.049 1 1 2 "Peanuts-butter", "Market basket data"
13 Baked, 0.049 1 1 "Market basket data"
14 Boiled, 0.049 1 1 "Market basket data"
404 04003NA,11, 0.000965 1 1 0 "Pears-juice", "1997 PDP"
405 15008AA,6B, 0.000033 1 1 0 "Peas-succulent/blackeye/cowpea", "PDP 1996"
407 14023AA,1AB, 0.00034 1 1 0 "Radishes-japanese (daiken)", "FDA"
413 15009AB,6A, 0.000033 1 1 0 "Snowpeas", "PDP 1996"
416 01016JA,O, 0.00022 0.3 1 0 "Strawberries-juice", "FDA data"
417 15018HA,O, 0.00046 1 1 0 "Sunflower-seeds", "acute AR * 1% crop treated"
418 14018LV,2, 0.001211 1 1 0 "Sweet potatos-leaves", "PDP 1994-1997"
420 02008JC,10, 0.001 3.2 1 0 "Tangerines-juice-concentrate", "MBS orange juice 10% CT"
423 11005DA,8, 0.0044 14.3 1 0 "Tomatoes-dried", "PDP "
431 030090L,14, 0.02 1 1 0 "Walnut oil", "Field trials from Walnuts and Almonds"
437 24007OL,15, 0.0032 1 1 0 "Wheat-germ oil", "PDP 1995-1997"
441 02002JC,10, 0.001 4 1 0 "Grapefruit-juice-concentrate", "MBS orange juice 10% CT"
442 02004JC,10, 0.001 11.4 1 0 "Lemons-juice-concentrate", "MBS orange juice 10% CT"
443 02005JC,10, 0.001 6 1 0 "Limes-juice-concentrate", "MBS orange juice 10% CT"
448 02002HA,10, 0.000914 1 1 0 "Grapefruit peel", "Translated from oranges"
449 No Code,P, 0.000001 1 1 0 "Turkey-other organ meats", "Dietary Burden Calculation"
451 No Code,5A, 0.001486 1 1 0 "Broccoli-chinese", "PDP 94 from broccoli"

452	No Code,5B,	0.0015	1	1	0	"Bok choy", "FDA data"
480	06016GA,O,	0.000424	1	1	0	"Plantains-green", "PDP 94 and 95"
481	06016DA,O,	0.000424	3.9	1	0	"Plantains-dried", "PDP 94 and 95"
482	No Code,O,	0.00032	1	1	0	"Soybeans-protein isolate", "Knizner Memo."
484	No Code,O,	0.00034	1	1	0	"Radishes-oriental", "FDA"
940	No Code,O,	0.000022	1	1	0	"Peanuts-hulled", "Peanut butter data."

Appendix D: DAS Drinking Water Risk Assessment Position

D.1. Termiticidal Use

D.1.1. Appropriate Scenario for Exposure Assessment

Private drinking water wells have become contaminated through *accidental movement* of termiticides from the intended structural application site(s) into wells located largely (75%) within 30 feet of the structure (Thomas and Chambers, 1997). This situation falls into the category of an unintended event requiring remediation, rather than a standard scenario of a pesticide use pattern suitable for exposure assessment. An analogous case is the difference between accidental direct treatment of a surface water body by an aerial applicator and deposition into the same water body resulting from unintended spray drift during a legal aerial application. The latter event constitutes the scenario for exposure assessment, while the former calls for corrective action. From this perspective, the rare accidental well contamination coming from termiticide applications (see section D.1.4.) does not belong in the risk assessment, particularly as remediation routinely occurs following such accidents (Poletika et al., 1999) with no significant exposure to residents.

D.1.2. Likelihood of Consumption of Contaminated Water

Poletika et al. (1999) explained the transport mechanism for well contamination by chlorpyrifos and all other liquid barrier termiticide treatments: saturated flow through unanticipated preferential flow channels at the time of application. The minimum dilution for an initial chlorpyrifos termiticide treatment recommended on the label is 0.75%. At this level of dilution, the mixture of liquid product and water takes the form of a milky white emulsion. It is probable that the volume of emulsion entering the contaminated well delivers a milky white liquid when well water flows through the domestic tap soon after application, thus alerting the resident that something is amiss. Chlorpyrifos is also known to cause a change in the smell of water when present. In fact, an off-smell in the water is the most frequently cited reason by residents in our Water Incident Survey for suspecting a chlorpyrifos contamination to their drinking water (Thomas and Chambers, 1997).

It is also important to note that structural termite treatments are a major event in the life of a resident - both from an inconvenience perspective as well as a significant and usually unplanned out-of-pocket expense. As such, most residents will likely be more observant of changes to their surroundings (i.e., odor/off-color in their drinking water) post-application.

All of these factors work together to ensure that residents experiencing well contamination events do not consume contaminated water prior to entering the well remediation program.

D.1.3. DAS's Stewardship Policy

The following description of the DAS product stewardship policy is taken from page 122 of Poletika et al. (1999):

> "*Although the frequency of well contamination is low (Thomas and Chambers, 1997, MRID 44235001), Dow AgroSciences recognizes there is the potential for adverse human health effects in a small sub-population of the U.S. and has voluntarily implemented a product stewardship program that minimizes exposure of affected residents to chlorpyrifos residues in drinking water wells. This program is centered on a comprehensive remediation procedure carried out by professional applicators. Immediately upon notification by the homeowner, the applicator advises the homeowner to cease using suspected contaminated water until after remediation and analytical confirmation of water is conducted showing acceptability for consumption (based on the published EPA HAL). Decontamination is initiated by superchlorination of the well water. Simultaneously, an activated charcoal filter is placed on the supply line to the household water tap. Following completion of this procedure, there is no exposure level or duration that is significant relative to any meaningful toxicity threshold value and the well is restored to its previous condition.*"

Well samples continue to be collected and analyzed until the measured concentration declines to the analytical LOQ (presently 100 ng/L). Therefore, residents will be exposed to a maximum chronic exposure concentration of 100 ng/L after well remediation is completed. A properly installed, fresh carbon filter will reduce exposure levels considerably below 100 ng/L.

D.1.4. Decline in Recent Incident Reports

Over the past year and one-half the annual average number of well contamination incidents has declined from 30 prior to 1997 to about eight since 1998. This decline is probably due to implementation of industry-wide termiticide product general label improvement through publication of EPA PRN 96-7 and the commercialization of the Sentricon* *Termite Colony Elimination System*. Eight incidents in one year relative to the hundreds of thousands of applications performed represents a very low frequency of occurrence, with all reported incidents remediated as described above.

D.2. Historical Occurrence of OP Insecticides in Waters of the United States

Christensen and Dando (1999) conducted a comprehensive review of ground and surface water monitoring data for chlorpyrifos and four other OP insecticides for the period 1990-1997. This temporal window was selected because it represents current use patterns and collects data generated by analytical methods more sensitive than those typically used in older studies. Data sources were SDWA compliance monitoring data from 14 high use states, USGS NAWQA data from 20 study units, US EPA STORET, data from state agencies, and results of a literature search.

DAS submits, by reference to the existing MRID number, this study in support of our risk assessment position. Specifically, DAS asserts that the study confirms the low incidence of chlorpyrifos detections in source water and demonstrates no detections in drinking water. Because the scope of the study includes several data sets besides the NAWQA data, in particular data from states identified as representing high use areas, it also contributes new monitoring information in vulnerable regions. A brief summary of the important study findings follows.

No detections were reported for chlorpyrifos in 4,267 SDWA samples. In the STORET drinking water database, there were no detections in 99 samples analyzed for chlorpyrifos. USGS NAWQA monitored 33,482 non-drinking water samples in 20 NAWQA Study Units. Detections for chlorpyrifos totalled 1,177 (3.5%), and the maximum detected concentration was 0.4 μg/L.

The STORET non-drinking water database for the five OP insecticides in the study contains 19,842 samples collected from 41 states, Guam, the Northern Mariana Islands, and Puerto Rico. There were 228 detections reported for chlorpyrifos, and the maximum concentration was 1.7 μg/L. State agency data from 10 states aggregated to 26,713 non-drinking water monitoring samples for the five OP insecticides in the study. There were 253 reported detections for chlorpyrifos, and the maximum concentration was 3.7 μg/L. The literature search captured 7,262 monitoring samples for the five OP insecticides in the study. All detections occurred only in surface water. There were 98 chlorpyrifos detections, and the maximum concentration was 0.15 μg/L.

The 99th percentile concentration for chlorpyrifos detections in all drinking and non-drinking water samples was 0.525 μg/L, based on a non-detection of one-half the LOQ. In drinking water samples, the maximum was less than the method LOQ. These reported concentrations from the extreme tail of the sample data distribution support the acute concentrations proposed in Corrected Table 6 above. The large number of non-detects suggest that the low levels proposed for chronic exposure are also more appropriate than the original EFED recommendations. Because these data exclude accidental movement of termiticides into drinking water wells, they are useful for estimating groundwater concentrations resulting from leaching of correctly applied treatments. Thus, there is no reason to distinguish between termiticide and non-termiticide use areas. The monitoring data integrate all uses.

Appendix E: DAS Comments on Agricultural and Occupational Exposure Assessment – Mar-Quest Market Research Study

Very little chlorpyrifos specific use pattern information at the level of the end user has existed in the past. Given the lack of such specific information, inputs for risk assessments were often taken from insecticide generic use databases or extrapolated from crop or agricultural use scenarios. To help provide a better understanding of actual chlorpyrifos urban pest market usage, DAS commissioned a small qualitative market research study by Mar-Quest in 1999. The information from this survey can be used to further advance risk assessments for these uses. DAS recognizes the challenges of interpreting the many varied uses in this market, and offers our assistance to EPA in analyzing and understanding our labels, typical use patterns, and the survey data in more detail.

Although this study has a small number of surveys per market segment (i.e., 11-14), DAS is of the opinion that, with very few exceptions, the median and mean responses fairly represent what we believe to be typical use in the field given our professional experience selling chlorpyrifos for over 30 years. It should be noted that the methods DAS used to obtain chlorpyrifos users was to ask our sales representatives to send in names of 10-15 customers per market segment that we knew were users of chlorpyrifos. This request tried to incorporate users that ranged from small to large company operations. From these lists, as many customers were surveyed as possible.

DAS recognizes there was one question in the survey which was poorly designed and, thus, the answers obtained from the question are not used in our comments to the EPA. This question was "What is your percent split in the use of the average rate versus the maximum rate per acre (or per 100 gallons) of chlorpyrifos or Dursban*." This question intended to accommodate the multiple use pattern sites/pests on our labels, each of which has a minimum and maximum use rate. The respondents misinterpreted this question by superimposing their response for the label's maximum use rate for one use site/pest on to the maximum use rates for other sections of the label's use sites/pests and, since these maximum use rates differed from each other, the responses inaccurately reflect information specific to each use site/pest. Although included in the final

survey results, DAS believes the results for this particular question are not accurate and should not be used. In addition, frequency of use information is collected as verbal commentary and was unable to be quantified ,although general trends can be inferred from the comments.

Example for maximum rate question: Dursban labels for insect control on turfgrass are split into two rate sections, surface feeders and subsurface feeders. The rate range for surface feeders is 1-2 lb a.i./acre and 2-4 lb a.i./acre for subsurface feeding insects. The answer to the maximum use rate question was that on average, 62% of the time the use rate is the average rate/acre and 31% of the time it is the maximum rate per acre. Does this mean then that 31% of the time 2 lb a.i./acre is used for surface feeders, or, 31% of the time 4 lb a.i./acre is used for subsurface feeders? Or, does it mean that 31% of the time 4 lb a.i./acre is used in general even though the 4 lb a.i./acre rate is specific to subsurface feeders and is not applicable to surface feeders? The question should have been asked separately for each rate range section on the label to be meaningful; it will be redesigned in future studies.

To DAS's knowledge, this is the only chlorpyrifos specific use data collected in a manner to meet the needs of risk assessments that exists for urban market segments, allowing the refinement of the risk assessment beyond that possible using generic information. In the future, given availability of funding, DAS will use the learnings from this qualitative study to better structure questions to be incorporated into larger, more quantitative market research studies as appropriate.

QUALITATIVE RESEARCH ON THE LABELED APPLICATION AND USE OF CHLORPYRIFOS BY PROFESSIONAL MARKETS

July, 1999

PROJECT NO. 561-9

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EXECUTIVE SUMMARY

BACKGROUND AND OBJECTIVES

Dow AgroSciences was interested in obtaining qualitative information from a broad number of professional market segments regarding application rates and frequencies for labeled uses of chlorpyrifos. More specifically, a qualitative probe market research study was undertaken to obtain chlorpyrifos use information that could augment risk assessments. In addition, this information is valuable to set the stage for a more quantitative market research study in the future if this need were to arise. Questions primarily focused on understanding the labeled average use rates, volume of product handled, frequency of application, and specifics about product use for select market segments (i.e., fire ant quarantine, etc.).

METHODOLOGY

A total of 100 interviews were conducted among EIGHT different market segments in late May, 1999 and early June, 1999, as follows:

TABLE 1
SAMPLE DISPOSITION
(n=all respondents)

TARGET AUDIENCE	**NUMBER OF RESPONDENTS**
Pest Control Operator (PCO)	13
Lawn Care Operator (LCO)	13
Golf Courses	12
Sod Farms	13
Landscape	12
Nursery	14
Arborists	11
Greenhouse	12
Total	100

The following issues are important to note from a research standpoint:

- The lists of chlorpyrifos users were provided by Dow AgroSciences, with Mar-Quest Research qualifying each respondent as being a user of Dursban* and/or other DAS chlorpyrifos formulations. The interview was conducted with the person that was considered to be most knowledgeable about the application rates and applicator behavior patterns (e.g., Technical Director, Owner, General Manager, Golf Course Superintendent, etc.).

- The results should be considered "qualitative" due to the small sample size. Therefore, the findings must be carefully used to accurately represent the industry. However, the results should be a positive addition to the Dow AgroSciences database to begin to understand labeled usage and exposure patterns for chlorpyrifos.

For each of the market segments, the data is broken down by geography in terms of respondents in the eastern part of the United States (east of the Mississippi River) and respondents in the western part of the United States (west of the Mississippi), in addition to the combined total. This split represents industry demographics for the pest control market. A more appropriate split for the turf and ornamental markets is north and south and this will be accommodated in future studies as needed. Caution should be in order when examining any differences between the two geographical groups, since the bases (e.g., number of respondents in each group) were very small.

SUMMARY OF DATA

Following is a summary of the data highlights for each of the separate target professional markets for the labeled use of chlorpyrifos:

PROFESSIONAL PEST CONTROL OPERATORS

PCO – FORMULATION USE FOR PERIMETER TREATMENTS (Company)

ISSUES (source)	DEFINITION	%
Percentage using each formulation (Table 2)	EC only WP only Both EC/WP	23% 39% 39%

PCO - PERIMETER TREATMENT DATA (Applicator)

ISSUES (source)	DEFINITION	MEDIAN
Time spent treating an average structure (Table 3)	Minutes/structure Days/week Weeks/month	20 5.0 4
Average concentration of chlorpyrifos (Table 4)	Formulation (EC) Formulation (WP)	0.38% 0.03%
Average volume of chlorpyrifos applied (Table 5)	Gallons	18.0
Average number of structures treated (Table 6)	Structures/day	8

PCO – SINGLE FAMILY RESIDENCES – INTERIOR (Company)

ISSUES (source)	DEFINITION	%
Percentage using EC chlorpyrifos (Table 8)	Single family residences	62%

PCO – SINGLE FAMILY RESIDENCE DATA – INTERIOR (Applicator)

ISSUES (source)	DEFINITION	MEDIAN
Time spent treating an average structure (Table 9)	Minutes/structure Days/week Weeks/month	20 5.0 4
Average concentration of chlorpyrifos applied (Table 10)	Concentration	0.50%
Volume of chlorpyrifos applied (Table11)	Gallons	0.25
Average number of structures treated (Table 12)	Structures/day	7.5

PCO – MULTI-FAMILY RESIDENCES – INTERIOR (Company)

ISSUES (source)	DEFINITION	%
Percentage using EC chlorpyrifos (Table 13)	Multi-family residences	54%

PCO – MULTI-FAMILY FAMILY RESIDENCE DATA – INTERIOR (Applicator)

ISSUES (source)	DEFINITION	MEDIAN
Time spent treating an average structure (Table 14)	Minutes/structure Days/week Weeks/month	30 5.0 4
Average concentration of chlorpyrifos applied (Table 15)	Concentration	0.50%
Volume of chlorpyrifos applied (Table16)	Gallons	2.0
Average number of structures treated (Table 17)	Structures/day	2.0

PCO – COMMERCIAL APPLICATIONS – INTERIOR (Company)

ISSUES (source)	DEFINITION	%
Percentage using EC chlorpyrifos (Table 18)	Commercial applications	46%

PCO – COMMERCIAL **FOOD** APPLICATION DATA – INTERIOR (Applicator)

ISSUES (source)	DEFINITION	MEDIAN
Time spent treating an average structure (Table 19)	Minutes/structure Days/week Weeks/month	40 5.0 4
Average concentration of chlorpyrifos applied (Table 20)	Concentration	0.55%
Volume of chlorpyrifos applied (Table 21)	Gallons	1.00
Average number of structures treated (Table 22)	Structures/day	3

PCO – COMMERCIAL **NON-FOOD** APPLICATION DATA – INTERIOR (Applicator)

ISSUES (source)	DEFINITION	MEDIAN
Time spent treating an average structure (Table 19)	Minutes/structure Days/week Weeks/month	20 5.0 4
Average concentration of chlorpyrifos applied (Table 20)	Concentration	0.50%
Volume of chlorpyrifos applied (Table 21)	Gallons	0.63
Average number of structures treated (Table 22)	Structures/day	3

PROFESSIONAL LAWN CARE OPERATORS

LCO – FORMULATION USE FOR TURFGRASS SURFACE FEEDERS (Company)

ISSUES (source)	DEFINITION	%
Percentage using each formulation (Tables 23, 25, 27)	Liquid WP Granular	54% 8% 39%

LCO – FORMULATION DATA FOR TURFGRASS SURFACE FEEDERS (Applicator)

ISSUES (source)	DEFINITION	MEDIAN
Liquid (Table 24)	Lbs ai/acre Acres/day Days/year	1.0 2.50 30
WP (Table 26)	Lbs ai/acre Acres/day Days/year	1 2.25 16
Granular (Table 28)	Lbs ai/acre Acres/day Days/year	0.75 4.0 30

LCO – FORMULATION USE FOR TURFGRASS SUBSURFACE FEEDERS (Company)

ISSUES (source)	DEFINITION	%
Percentage using each formulation (Tables 29, 31, 33)	Liquid WP Granular	15% 8% 8%

LCO – FORMULATION DATA FOR TURFGRASS SUBSURFACE FEEDERS (Applicator)

ISSUES (source)	DEFINITION	MEDIAN
Liquid (Table 30)	Lbs ai/acre Acres/day Days/year	0.97 1 28
WP (Table 32)	Lbs ai/acre Acres/day Days/year	1 1 30
Granular (Table 34)	Lbs ai/acre Acres/day Days/year	1 1 5

LCO – AVERAGE VERSUS MAXIMUM RATE (Company)

ISSUES (source)	DEFINITION	MEAN
Rate applied (Table 35)	Average rate/acre Maximum rate/acre	62% 31%

LCO – DILUTE SPRAY VOLUME (Company)

ISSUES (source)	DEFINITION	MEDIAN
Average dilute spray volume (Table 36)	Gallons/acre	120

GOLF COURSES

GOLF COURSES – FORMULATION USE FOR TURFGRASS SURFACE FEEDERS
(Company)

ISSUES (source)	DEFINITION	%
Percentage using each formulation (Tables 37, 39, page 51)	Liquid WP Granular	75% 8% 0%

GOLF COURSES – FORMULATION DATA FOR TURFGRASS SURFACE FEEDERS
(Applicator)

ISSUES (source)	DEFINITION	MEDIAN
Liquid (Table 38)	Lbs ai/acre Acres/day Days/year	1.00 3.7 6
WP (Table 40)	Lbs ai/acre Acres/day Days/year	na* 3 7

*Don't know/no opinion

GOLF COURSES – FORMULATION USE FOR TURFGRASS SUBSURFACE FEEDERS
(Company)

ISSUES (source)	DEFINITION	%
Percentage using each formulation (Table 41, page 54, Table 43)	Liquid WP Granular	58% 0% 8%

GOLF COURSES – FORMULATION DATA FOR TURFGRASS SUBSURFACE FEEDERS
(Applicator)

ISSUES (source)	DEFINITION	MEDIAN
Liquid (Table 42)	Lbs ai/acre Acres/day Days/year	1.0 3.00 4
Granular (Table 44)	Lbs ai/acre Acres/day Days/year	na* 150 2

*Don't know/no opinion

GOLF COURSES – AVERAGE VERSUS MAXIMUM RATE (Company)

ISSUES (source)	DEFINITION	MEAN
Rate applied (Table 45)	Average rate/acre Maximum rate/acre	65% 35%

GOLF COURSES – DILUTE SPRAY VOLUME (Company)

ISSUES (source)	DEFINITION	MEDIAN
Average dilute spray volume (Table 46)	Gallons/acre	64

SOD FARMS

SOD FARMS – FORMULATION USE FOR TURFGRASS SURFACE FEEDERS (Company)

ISSUES (source)	DEFINITION	%
Percentage using each formulation (Tables 47, 49)	Liquid WP Granular (not labeled)	23% 46% 0%

SOD FARMS – FORMULATION DATA FOR TURFGRASS SURFACE FEEDERS (Applicator)

ISSUES (source)	DEFINITION	MEDIAN
Liquid (Table 48)	Lbs ai/acre Acres/day Days/year	2 20 3
WP (Table 50)	Lbs ai/acre Acres/day Days/year	1.3 16 5

SOD FARMS – FORMULATION USE FOR TURFGRASS SUBSURFACE FEEDERS (Company)

ISSUES (source)	DEFINITION	%
Percentage using each formulation (Tables 51, 53)	Liquid WP Granular (not labeled)	15% 23% 0%

SOD FARMS – FORMULATION DATA FOR TURFGRASS SUBSURFACE FEEDERS (Applicator)

ISSUES (source)	DEFINITION	MEDIAN
Liquid (Table 52)	Lbs ai/acre Acres/day Days/year	2 18 4
WP (Table 54)	Lbs ai/acre Acres/day Days/year	3 25 7

SOD FARMS – PERCENTAGE PERFORMING FIRE ANT QUARANTINE APPLICATIONS (Company)

ISSUES (source)	DEFINITION	%
Fire ant quarantine applications (Table 55)	50W at the 8 lb. ai/acre rate	54%

SOD FARMS – FIRE ANT QUARANTINE APPLICATION DATA (Applicator, Worker)

ISSUES (source)	DEFINITION	MEDIAN
Dursban 50W applied (Table 56)	Acres/day Days/year	175 6
Sod treated with 50W processed by hand (Table 57)	Acres/day Days/year	1.0 120

SOD FARMS – AVERAGE VERSUS MAXIMUM RATE (Company)

ISSUES (source)	DEFINITION	MEAN
Rate applied (Table 58)	Average rate/acre Maximum rate/acre	48% 52%

SOD FARMS – DILUTE SPRAY VOLUME (Company)

ISSUES (source)	DEFINITION	MEDIAN
Average dilute spray volume (Table 59)	Gallons/acre	35

LANDSCAPERS

LANDSCAPERS – FORMULATION USE FOR ORNAMENTAL INSECTS (Company)

ISSUES (source)	DEFINITION	%
Percentage using each formulation (Tables 60, 62, 64)	Liquid WP Granular	67% 33% 25%

LANDSCAPERS – FORMULATION DATA FOR ORNAMENTAL INSECTS (Applicator)

ISSUES (source)	DEFINITION	MEDIAN
Liquid (Table 61)	Lbs ai/100 gallons Dilute gallons/day Days/year	0.50 75 22
WP (Table 63)	Lbs ai/100 gallons Dilute gallons/day Days/year	0.25 55 70
Granular (Table 65)	Lbs ai/acre Acres/day Days/year	1 2.00 4

LANDSCAPERS – AVERAGE RATE VERSUS MAXIMUM RATE (Company)

ISSUES (source)	DEFINITION	MEAN
Rate applied (Table 66)	Average rate/100 gallons Maximum rate/100 gallons	40% 60%

LANDSCAPERS – DILUTE SPRAY VOLUME (Company)

ISSUES (source)	DEFINITION	MEDIAN
Average dilute spray volume (Table 67)	Gallons/acre	23

LANDSCAPERS – ACRES TREATED (Company)

ISSUES (source)	DEFINITION	MEDIAN
Average number of acres treated (Table 68)	Acres/year	27

LANDSCAPERS – PERCENTAGE PERFORMING SPECIFIC TREATMENTS (Company)

ISSUES (source)	DEFINITION	MEAN
Percentage of use (Table 69)	Trees – bark beetles	38%
	Cut stumps – pine weevils	2%
	Soil – ornamental insects	3%
	Pine seedlings – pine weevils	1%
	Dormant treatment	15%
	Soil of containers	0%
	Other treatments	42%

LANDSCAPERS – SPECIFIC TREATMENT DATA (Applicator)

ISSUES (source)	DEFINITION	MEDIAN
Average dilute gallons/day used (Table 70)	Trees – bark beetles	50
	Cut stumps – pine weevils	150
	Soil – ornamental insects	na*
	Pine seedlings – pine weevils	na*
	Dormant treatment	325
	Soil of containers	na**
	Other treatments	na*
Days/year Dursban applied (Table 71)	Trees – bark beetles	18
	Cut stumps – pine weevils	5
	Soil – ornamental insects	10
	Pine seedlings – pine weevils	2
	Dormant treatment	10
	Soil of containers	na**
	Other treatments	na*

*Use varied/not specified
**None of the landscapers were performing this treatment

NURSERIES

NURSERIES – FORMULATION USE FOR ORNAMENTAL INSECTS (Company)

ISSUES (source)	DEFINITION	%
Percentage using each formulation (Tables 72, 74)	Liquid	36%
	WP	94%
	Granular (not labeled)	0%

NURSERIES – FORMULATION DATA FOR ORNAMENTAL INSECTS (Applicator)

ISSUES (source)	DEFINITION	MEDIAN
Liquid (Table 73)	Lbs ai/100 gallons Dilute gallons/day Days/year	0.37 400 12
WP (Tables 75A/75B)	Lbs ai/100 gallons Dilute gallons/day Days/year	0.50 400 25

NURSERIES – AVERAGE RATE VERSUS MAXIMUM RATE (Company)

ISSUES (source)	DEFINITION	MEAN
Rate applied (Table 76)	Average rate/100 gallons Maximum rate/100 gallons	56% 44%

NURSERIES – DILUTE SPRAY VOLUME (Company)

ISSUES (source)	DEFINITION	MEDIAN
Average dilute spray volume (Table 77)	Gallons/acre	175

NURSERIES – ACRES TREATED (Company)

ISSUES (source)	DEFINITION	MEDIAN
Average number of acres treated (Table 78)	Acres/year	33

NURSERIES – PERCENTAGE PERFORMING SPECIFIC TREATMENTS (Company)

ISSUES (source)	DEFINITION	MEAN
Percentage of use (Table 79)	Trees – bark beetles Cut stumps – pine weevils Soil – ornamental insects Pine seedlings – pine weevils Dormant treatment Soil of containers Other treatments	5% 0% 10% 0% 21% 9% 55%

NURSERIES – SPECIFIC TREATMENT DATA (Applicator)

ISSUES (source)	DEFINITION	MEDIAN
Average dilute gallons/day used (Table 80)	Trees – bark beetles	100
	Cut stumps – pine weevils	na*
	Soil – ornamental insects	92.5
	Pine seedlings – pine weevils	na*
	Dormant treatment	625.0
	Soil of containers	58
	Other treatments	400
Days/year Dursban applied (Table 81)	Trees – bark beetles	6
	Cut stumps – pine weevils	na*
	Soil – ornamental insects	9
	Pine seedlings – pine weevils	na*
	Dormant treatment	23
	Soil of containers	3
	Other treatments	20

*None of the nurseries were performing this treatment

ARBORISTS

ARBORISTS – FORMULATION USE FOR ORNAMENTAL INSECTS (Company)

ISSUES (source)	DEFINITION	%
Percentage using each formulation (Tables 82, 84, page 109)	Liquid	64%
	WP	64%
	Granular	0%

ARBORISTS – FORMULATION DATA FOR ORNAMENTAL INSECTS (Applicator)

ISSUES (source)	DEFINITION	MEDIAN
Liquid (Table 83)	Lbs ai/100 gallons	0.75
	Dilute gallons/day	350
	Days/year	13
WP (Table 85)	Lbs ai/100 gallons	0.75
	Dilute gallons/day	225
	Days/year	17

ARBORISTS – AVERAGE RATE VERSUS MAXIMUM RATE (Company)

ISSUES (source)	DEFINITION	MEAN

Rate applied (Table 86)	Average rate/100 gallons Maximum rate/100 gallons	71% 29%

ARBORISTS – DILUTE SPRAY VOLUME (Company)

ISSUES (source)	DEFINITION	MEDIAN
Average dilute spray volume (Table 87)	Gallons/acre	296

ARBORISTS – ACRES TREATED (Company)

ISSUES (source)	DEFINITION	MEDIAN
Average number of acres treated (Table 88)	Acres/year	188

ARBORISTS – PERCENTAGE PERFORMING SPECIFIC TREATMENTS (Company)

ISSUES (source)	DEFINITION	MEAN
Percentage of use (Table 89)	Trees – bark beetles Cut stumps – pine weevils Soil – ornamental insects Pine seedlings – pine weevils Dormant treatment Soil of containers Other treatments	26% 3% 1% 0% 5% 0% 66%

ARBORISTS – SPECIFIC TREATMENT DATA (Applicator)

ISSUES (source)	DEFINITION	MEDIAN
Average dilute gallons/day used (Table 90)	Trees – bark beetles Cut stumps – pine weevils Soil – ornamental insects Pine seedlings – pine weevils Dormant treatment Soil of containers Other treatments	313 88 563 na* 5 na* 675
Days/year Dursban applied (Table 91)	Trees – bark beetles Cut stumps – pine weevils Soil – ornamental insects Pine seedlings – pine weevils Dormant treatment Soil of containers Other treatments	8 11 8 na* 30 na* 25

*None of the arborists were performing this treatment

GREENHOUSES

GREENHOUSES – FORMULATION USE FOR ORNAMENTAL INSECTS (Company)

ISSUES (source)	DEFINITION	%
Percentage using each formulation (page 120)	Liquid WP (not labeled) Granular (not labeled)	100% 0% 0%

GREENHOUSES – FORMULATION DATA FOR ORNAMENTAL INSECTS (Applicator)

ISSUES (source)	DEFINITION	MEDIAN
Liquid (Table 92)	Lbs ai/100 gallons Dilute gallons/day Days/year	0.66 100 22

GREENHOUSES – AVERAGE RATE VERSUS MAXIMUM RATE (Company)

ISSUES (source)	DEFINITION	MEAN
Rate applied (Table 93)	Average rate/100 gallons Maximum rate/100 gallons	43% 57%

GREENHOUSES – DILUTE SPRAY VOLUME (Company)

ISSUES (source)	DEFINITION	MEDIAN
Average dilute gallons per acre (Table 94)	Gallons/acre	155

GREENHOUSES – ACRES TREATED (Company)

ISSUES (source)	DEFINITION	MEDIAN
Average number of acres treated (Table 95)	Acres/year	21

GREENHOUSES – PERCENTAGE PERFORMING SPECIFIC TREATMENTS (Company)

ISSUES (source)	DEFINITION	MEAN
Percentage of use (Table 96)	Trees – bark beetles	0%
	Cut stumps – pine weevils	0%
	Soil – ornamental insects	0%
	Pine seedlings – pine weevils	0%
	Dormant treatment	na*
	Soil of containers	9%
	Other treatments	83%

*Don't know/no opinion

GREENHOUSES – SPECIFIC TREATMENT DATA (Applicator)

ISSUES (source)	DEFINITION	MEDIAN
Average dilute gallons/day used (Table 97)	Trees – bark beetles	na*
	Cut stumps – pine weevils	na*
	Soil – ornamental insects	na*
	Pine seedlings – pine weevils	na*
	Dormant treatment	na**
	Soil of containers	200
	Other treatments	100
Days/year Dursban applied (Table 98)	Trees – bark beetles	na*
	Cut stumps – pine weevils	na*
	Soil – ornamental insects	na*
	Pine seedlings – pine weevils	na*
	Dormant treatment	na**
	Soil of containers	10
	Other treatments	20

*None of the greenhouses were performing this treatment
**Don't know/no opinion

Table E.1. Passive Dosimetry: Maximum PPE Intermediate-Term Dermal, Inhalation, and Total MOEs for (Ag Uses) Chlorpyrifos

Exposure Scenario (Scenario #)	Dermal Unit Exposure (mg/lb ai)[a]	Inhalation Unit Exposure (µg/cm^2) [b]	Application Rate (lb ai/A)	Dermal - Maximum PPE [b, e]		Inhalation - Maximum PPE [c, e]		Total MOE
				Daily Dose (mg/kg/day)	MOE	Daily Dose (mg/kg/day)	MOE	
Mixer/Loader Exposure								
Mixing/loading liquids for aerial application (1a)	0.017	0.24	Predominant max 1.5	0.0038	26	0.0018	56	18
			Citrus 3.5	0.0026	39	0.0012	83	27
			Sodfarm 4.0	0.010	10	0.0048	21	7
Mixing/loading liquids for groundboom application (1b)			Predominant max 1.5	0.00087	114	0.00041	240	78
			Tobacco 5.0	0.0029	34	0.0014	73	23
			Sodfarm 8.0 (fire ant)	0.00058	172	0.00027	360	117
Mixing/loading liquids for airblast application (1c)			Citrus 6.0	0.0018	57	0.00082	120	39
			Predominant max 2.0	0.00058	172	0.00027	360	117
			Ornamental 4.0	0.00029	343	0.00014	730	233
Mixing WP for Aerial Application (2a)	0.13	8.6	Predominant max 2.0	0.039	3	0.086	1	0.8
			Sodfarm 4.0	0.078	1	0.17	0.6	0.4
			Citrus 6.0	0.12	5	0.26	2.3	2
Mixing WP for Groundboom Application (2b)			Predominant max (brassica) 1.0	0.0045	22	0.0098	10	7
			Sodfarm 8.0 (fire ant)	0.0045	22	0.0098	10	7
			Ornamental 4.0	0.0022	45	0.0049	20	14

Exposure Scenario (Scenario #)	Dermal Unit Exposure (mg/lb ai)[a]	Inhalation Unit Exposure (µg/cm^2) [b]	Application Rate (lb ai/A)	Dermal - Maximum PPE [b, e]		Inhalation - Maximum PPE [c, e]		Total MOE
				Daily Dose (mg/kg/day)	MOE	Daily Dose (mg/kg/day)	MOE	
Mixing WP for Airblast Application (2c)			Predominant max 2.0	0.0045	22	0.0098	10	7
			Citrus 6.0	0.013	7.5	0.029	3	2
Loading Granulars for Aerial Application (3a)	0.0034	0.34	Max. 1.95	0.00099	100	0.0033	30	23
Loading Granulars for Ground Application (3b)			Tobacco max. 3.0	0.00035	290	0.0012	86	66
			Corn typical 1.0	0.00012	860	0.00039	260	200
			Corn max 2.0	0.00023	430	0.00078	130	100
Mixing Dry Flowables for Aerial Application (4a)	0.047	0.15	Predominant max 2.0	0.014	7	0.0015	65	6
			Citrus 3.5	0.0071	14	0.00077	130	13
Mixing Dry Flowables for Groundboom Application (4b)			Predominant max 2.0	0.0032	31	0.00035	280	28
			Ornamental 4.0	0.0065	15	0.00070	140	14
Mixing Dry Flowables for Airblast Application (4c)			Predominant max 2.0	0.0016	62	0.00018	570	56
			Citrus 6.0	0.0048	21	0.00053	190	19
Applicator Exposure								
Aerial (Liquids) -- Enclosed Cockpit (5a)	See engineering controls	See engineering controls	See engineering controls	See engineering controls.	See engineering controls	See engineering controls	See engineering controls	See engineering controls
Aerial (Granulars) -- Enclosed Cockpit (5b)	See engineering controls	See engineering controls	See engineering controls	See engineering controls.	See engineering controls	See engineering controls	See engineering controls	See engineering controls

Exposure Scenario (Scenario #)	Dermal Unit Exposure (mg/lb ai)[a]	Inhalation Unit Exposure (µg/cm^2) [b]	Application Rate (lb ai/A)	Dermal - Maximum PPE [b, e]		Inhalation - Maximum PPE [c, e]		Total MOE
				Daily Dose (mg/kg/day)	MOE	Daily Dose (mg/kg/day)	MOE	
Groundboom Tractor (6)	See engineering controls	See engineering controls	See engineering controls	See engineering controls.	See engineering controls	See engineering controls	See engineering controls	See engineering controls
Airblast Applicator (7)	See engineering controls	See engineering controls	See engineering controls	See engineering controls.	See engineering controls	See engineering controls	See engineering controls	See engineering controls
Tractor-Drawn Granular Spreader (8)	0.0099 (baseline)	0.24	Tobacco max. 3.0	0.00043	231	0.00082	120	80
			Corn typical 1.0	0.00014	690	0.00027	360	240
			Corn max 2.0	0.00029	350	0.00055	180	120
Seed Treatment (9)	No Data	No Data	No Data	No Data	No Data	No Data	No Data	No Data
Dip Application (Preplant Peaches) (10)	No Data	No Data	No Data	No Data	No Data	No Data	No Data	No Data
Flagger Exposure								
Spray Applications (11)	0.011 (Baseline)	0.07	Predominant max 2.0	0.0030	33	0.00070	140	27
			Citrus 3.5	0.0015	67	0.00035	290	54
Granular Applications (12)	NA	NA	Max. 1.95	0.00047	214	0.00029	340	131
Mixer/Loader/Applicator Exposure								
Backpack Sprayer (13)	NA	NA	Predominant max 0.0417 lb ai/gal	0.0011	87	0.00014	700	78
			Bark beetle 0.08 lb ai/gal	0.0022	46	0.00027	360	41
			Citrus Bark 3.5	0.0024	42	0.00030	330	37
			Stump 0.16 lb ai/gal	0.0044	23	0.00055	180	20

Exposure Scenario (Scenario #)	Dermal Unit Exposure (mg/lb ai)[a]	Inhalation Unit Exposure (µg/cm^2) [b]	Application Rate (lb ai/A)	Dermal - Maximum PPE [b, e]		Inhalation - Maximum PPE [c, e]		Total MOE
				Daily Dose (mg/kg/day)	MOE	Daily Dose (mg/kg/day)	MOE	
			Animal premise 0.000052 lb ai/ft2	0.00004	2800	0.00000	22,000	2500
Low Pressure Handwand (14)	6.2	220	Predominant max 0.0417 lb ai/gal	0.0044	378	0.0052	700	240
			Bark beetle 0.08 lb ai/gal	0.0085	197	0.010	360	130
			Citrus Bark 3.5	0.0093	180	0.011	330	120
			Stump 0.16 lb ai/gal	0.017	99	0.020	180	64
			Animal premise 0.000052 lb ai/ft2	0.00001	12,000	0.00000	22,000	7,800
High Pressure Handwand (15)	1.6	24	Min. 0.0031 lb ai/gal	Min. 0.0021	47	0.0011	94	31
			Max. 0.0063 lb ai/gal	Max. 0.0043	23	0.0022	46	15
Tree Trunk Spray (16)	0.31	1	Citrus Bark 3.5	0.0093	11	0.0010	100	10
			Bark beetle 0.08 lb ai/gal	0.011	9	0.0011	88	9
			Pine seedling 0.16 lb ai/gal	0.021	4	0.0023	44	4
			Animal premise 0.000052 lb ai/ft2	0.00007	1,400	0.00001	13,000	1,300

[a] Max. PPE unit exposures represent the use of open systems (e.g., open pour mixing and open cab tractors) coveralls over long pants, long sleeved shirt, chemical-resistant gloves, and a dust/mist respirator (5-fold protection factor), except scenarios 8 and 11 which represents baseline dermal attire (i.e., long pants, long sleeved shirt, and no gloves) and a dust/mist respirator (5-fold protection factor).

[b] Max. PPE dermal daily dose (mg/kg/day) = [Maximum PPE dermal unit exposure (mg/lb ai) * Appl. rate (lb ai/acre) * Acres treated * 0.03 dermal absorption]/Body weight (70 kg).

[c] Max. PPE inhalation daily dose (mg/kg/day) = [inhalation unit exposure (mg/lb ai) * 0.001 µg/mg unit conversion * max appl rate (lb ai/A or lb ai/gal) * area treated (acres or gal) * 1 inhalation absorption]/Body weight (70 kg).

[e] MOE = NOAEL (mg/kg/day) / Daily Dose [Where Dermal NOAEL = 0.1 mg/kg/day and Inhalation NOAEL = 0.1 mg/kg/day]. MOE of 10 is considered acceptable.

[d] Max. PPE Total MOE = 1/((1/Dermal MOE) + (1/Inhalation MOE)).

Table E.2. Passive Dosimetry: Eng. Controls Intermediate-Term Dermal, Inhalation, and Total MOEs for (Ag Uses) Chlorpyrifos

Exposure Scenario (Scenario #)	Dermal Unit Exposure (mg/lb ai)	Inhalation Unit Exposure ($\mu g/cm^2$)	Application Rate (lb ai/A)	Dermal - Engineering Controls		Inhalation - Engineering Controls		Total MOE[i]
				Daily Dose (mg/kg/day) [a]	MOE[b]	Daily Dose (mg/kg/day)[d]	MOE[e]	
Mixer/Loader Exposure								
Mixing/loading liquids for aerial application (1a)	0.0086 (gloves)	0.083	Predominant max 1.5	0.0019	52	0.00062	160	39
			Citrus 3.5	0.0013	78	0.00042	240	59
			Sodfarm 4.0	0.0052	19	0.0017	60	15
Mixing/loading liquids for groundboom application (1b)			Predominant max 1.5	0.00044	230	0.00014	700	171
			Tobacco 5.0	0.0015	68	0.00047	210	51
			Sodfarm 8.0 (fire ant)	0.00029	340	0.00009	1,100	250
Mixing/loading liquids for airblast application (1c)			Citrus 6.0	0.00088	110	0.00028	350	86
			Predominant max 2.0	0.00029	340	0.00009	1,100	250
			Ornamental 4.0	0.00015	680	0.00005	2,100	510
Mixing WP for Aerial Application (2a)	0.0098 (gloves)	0.24	Predominant max 2.0	0.0029	34	0.0024	42	19
			Sodfarm 4.0	0.0059	17	0.0048	21	9
			Citrus 3.5	0.0015	68	0.0012	83	37
Mixing WP for Groundboom Application (2b)			Predominant max (brassica) 1.0	0.00034	300	0.00027	360	160
			Ornamental 4.0	0.00017	590	0.00014	730	330
			Sodfarm 8.0 (fire ants)	0.00034	300	0.00027	360	160

Exposure Scenario (Scenario #)	Dermal Unit Exposure (mg/lb ai)	Inhalation Unit Exposure (µg/cm^2)	Application Rate (lb ai/A)	Dermal - Engineering Controls		Inhalation - Engineering Controls		**Total MOE**[i]
				Daily Dose (mg/kg/day) [a]	MOE[b]	Daily Dose (mg/kg/day)[d]	MOE[e]	
Mixing WP for Airblast Application (2c)			Predominant max 2.0	0.00034	300	0.00027	360	160
			Citrus 6.0	0.0010	99	0.00082	120	55
Loading Granulars for Aerial Application (3a)	0.00017	0.034	Max. 1.95	0.00005	2000	0.00033	300	260
Loading Granulars for Ground Application (3b)			Tobacco max 3.0	0.00002	5,700	0.00012	860	740
			Corn typical 1.0	0.00001	17,000	0.00004	2,600	2,200
			Corn max 2.0	0.00001	8,500	0.00008	1,300	1,100
Mixing Dry Flowables for Aerial Application (4a)	Not Feasible	Not Feasible	Not Feasible	Not Feasible	Not Feasible	Not Feasible	Not Feasible	Not Feasible
Mixing Dry Flowables for Groundboom Application (4b)				Not Feasible	Not Feasible	Not Feasible	Not Feasible	Not Feasible
Mixing Dry Flowables for Airblast Application (4c)				Not Feasible	Not Feasible	Not Feasible	Not Feasible	Not Feasible
Applicator Exposure								
Aerial (Liquids) -- Enclosed Cockpit (5a)	0.005	0.068	Predominant max 2.0	0.0015	67	0.00068	150	46
			Citrus 3.5	0.00075	130	0.00034	290	92
Aerial (Granulars) -- Enclosed Cockpit (5b)	0.0016	1.3	Max. 1.95	0.00047	210	0.013	8	7
Groundboom Tractor (6)	0.005	0.043	Predominant max 1.5	0.00026	390	0.00007	1,400	300

Exposure Scenario (Scenario #)	Dermal Unit Exposure (mg/lb ai)	Inhalation Unit Exposure (µg/cm^2)	Application Rate (lb ai/A)	Dermal - Engineering Controls		Inhalation - Engineering Controls		**Total MOE**[i]
				Daily Dose (mg/kg/day) [a]	MOE[b]	Daily Dose (mg/kg/day)[d]	MOE[e]	
			Tobacco 5.0	0.00086	120	0.00025	410	91
			Sodfarm 8.0	0.0014	73	0.00039	250	57
Airblast Applicator (7)	0.019 (gloves)	0.45	Typical 2.0	0.00065	150	0.00051	190	86
			Citrus 6.0	0.0020	51	0.0015	65	29
			Ornamental Bark 4.0	0.00033	307	0.00026	390	170
Tractor-Drawn Granular Spreader (8)	NA	NA	Tobacco max. 3.0	0.00022	460	0.00075	130	100
			Corn typical 1.0	0.00007	1,400	0.00025	400	310
			Corn max 2.0	0.00014	700	0.00050	200	150
Seed Treatment (9)	No Data	No Data	No Data	No Data	No Data	No Data	No Data	No Data
Dip Application (Preplant Peaches) (10)	No Data	No Data	No Data	No Data	No Data	No Data	No Data	No Data
Flagger Exposure								
Spray Applications (11)	0.00022	0.007	Typical 2.0	0.00007	1,500	0.00007	1,400	730
			Citrus 3.5	0.00003	3000	0.00004	2,900	1,500
Granular Applications (12)	NA	NA	NA	0.00002	6,100	0.00003	3,400	2,200
Mixer/Loader/Applicator Exposure								
Backpack Sprayer (13)	Not Feasible	Not Feasible	Not Feasible	Not Feasible	Not Feasible	Not Feasible	Not Feasible	Not Feasible
Low Pressure Handwand (14)	Not	Not	Not Feasible	Not Feasible	Not	Not Feasible	Not	Not

Exposure Scenario (Scenario #)	Dermal Unit Exposure (mg/lb ai) Feasible	Inhalation Unit Exposure ($\mu g/cm^2$) Feasible	Application Rate (lb ai/A)	Dermal - Engineering Controls		Inhalation - Engineering Controls		Total MOE[i] Feasible
				Daily Dose (mg/kg/day) [a]	MOE[b] Feasible	Daily Dose (mg/kg/day)[d]	MOE[e] Feasible	
High Pressure Handwand (15)	Not Feasible	Not Feasible	Not Feasible	Not Feasible	Not Feasible	Not Feasible	Not Feasible	Not Feasible
Tree Trunk Spray (16)	Not Feasible	Not Feasible	Not Feasible	Not Feasible	Not Feasible	Not Feasible	Not Feasible	Not Feasible

[a] Engineering control unit exposures represent long pants, long sleeved shirt, and no gloves (exception - scenarios 1a, 1b, 1c, 2 a, 2b, 2c, and 7 represent handlers wearing chemical-resistant gloves) while using closed mixing systems (98 percent protection factor used for a closed granular loader) and enclosed cockpits/cabs.

[b] Engineering control dermal daily dose (mg/kg/day) = [Engineering Controls dermal unit exposure (mg/lb ai) * Appl. rate (lb ai/acre) * Acres treated * 0.03 dermal absorption] / Body weight (70 kg).

[c] Engineering control inhalation daily dose (mg/kg/day) = [Inhalation unit exposure (mg/lb ai) * 0.001 µg/mg unit conversion * max appl rate (lb ai/A or lb ai/gal) * area treated (acres or gal) * 1 inhalation absorption] / Body weight (70 kg).

[e] MOE = NOAEL (mg/kg/day)/Daily Dose [Where Dermal NOAEL = 0.10 mg/kg/day and Inhalation NOAEL = 0.1 mg/kg/day]. MOE of 10 is considered acceptable.

[d] Engineering control Total MOE = 1/((1/Dermal MOE) + (1/Inhalation MOE)).

Table E.3. Intermediate-Term Biological Monitoring for Agricultural Uses of Chlorpyrifos

Exposure Scenario (Number)[a]	Average Unit Dose[b] (mg/kg/lb ai)	Amount ai handled[c]		Clothing and Equipment Scenario Monitored	No. of Obs.	Daily Dose[d] (mg/kg/day)	MOE[e]
		Rate (lb ai/A)	Acres				
Mixer/Loader Risk							
Mixing Liquids for Aerial Application (1a)	3×10^{-6} (lognormal - geo mean)	1.5	350	Open pour liquids; cotton coveralls, cotton T-shirt, briefs, socks, eye protection, chemical-resistant nitrile gloves, chemical-resistant apron, and chemical-resistant knee high boots	14	0.0016	63
		4.0	350			0.0042	24
		3.5	100			0.0011	95
Mixing All Liquids for Groundboom Application (1b)	6.7×10^{-5}	1.5	80	Open pour liquids; cotton coveralls over T-shirt and briefs, rubber boots, baseball cap, and chemical resistant gloves	3	0.0080	12
Mixing All Liquids for Airblast Application (1c)	6.0×10^{-5}	1.5	40	Open pour liquids; denim coveralls over short-sleeved shirt, long-pants, T-shirt and briefs, chemical resistant gloves, and a respirator	15	0.0036	28
Mixing WP for Groundboom Application (2b)	3.9×10^{-4}	2.0	80	Open pour wettable powder; cotton coveralls over T-shirt and briefs, rubber boots, baseball cap, chemical resistant gloves, and ½ face respirator	6	0.062	1.6
Applicator Risk							
Groundboom Tractor (6)	6.1×10^{-5}	2.0	80	Open cab; cotton coveralls over T-shirt and briefs, and baseball cap	9	0.0098	10
Airblast (7)	9.1×10^{-5}	2.0	40	Open cab; denim coveralls over short-sleeved shirt, long-pants, T-shirt and briefs, chemical resistant gloves, and a respirator	15	0.0073	14
Mixer/Loader/Applicator Risk							

Table E.3. Intermediate-Term Biological Monitoring for Agricultural Uses of Chlorpyrifos

Exposure Scenario (Number)[a]	Average Unit Dose[b] (mg/kg/lb ai)	Amount ai handled[c]		Clothing and Equipment Scenario Monitored	No. of Obs.	Daily Dose[d] (mg/kg/day)	MOE[e]
		Rate (lb ai/A)	Acres				
Granular Loading Combined with Tractor-Drawn Spreader (Scenarios 3b and 8 combined)	1.0×10^{-5}	Typ. 1.0 Max 2.0	80	enclosed cab, various configurations of closed windows to open doorways; cotton coveralls over T-shirt and briefs, socks and shoes	12	0.0008 0.0016	125 63
Backpack (Greenhouse) (13)	2.7×10^{-3}	0.0417 lb ai/gal	40	Solo backpack sprayer; cotton coveralls over T-shirt and briefs, rubber boots, baseball cap, and chemical resistant gloves	2	0.0045	22
Low Pressure Handwand (Greenhouse) (14)	1.7×10^{-3}	0.0417 lb ai/gal	40	Gilmour 101P, manual sprayer; cotton coveralls over T-shirt and briefs, rubber boots, baseball cap, and chemical resistant gloves	1	0.0028	35
High Pressure Handwand (Greenhouse) (15)	3.7×10^{-3}	Min. 0.0031 lb ai/gal Max. 0.0063 lb ai/gal	1,000 gal/day	Six of the 13 test subjects wore neoprene rain jacket/pants, ¼ face respirator, face shield, cotton coveralls over T-shirt and briefs, and chemical resistant gloves. The remaining 7 test subjects wore cotton coveralls over T-shirt and briefs, and chemical resistant gloves.	13	Min. 0.011 Max. 0.023	Min. 9 Max. 4

[a] Data source for exposure scenarios 1a is MRID 447393-02; 1b, 2b, 6 is MRID No. 429745-01; exposure scenarios 1c and 7 is MRID No. 431381-02; exposure scenarios 13, 14, and 15 is MRID No. 430279-01; and exposure scenarios 3b and 8 combined is MRID No. 444835-01.

[b] All unit dose values are reported as the arithmetic means; except scenario 1a (lognormal -- geo. Mean). The results are reported as "unit doses" to extrapolate to the label maximum rates.

[c] Application rates are the maximum labeled rates found on EPA Reg. Nos. 62719-163, -39, -221, -23, -245, -255 -34 -79 -72 -166 -220; 34704-66; and greenhouse label 499-367. Not all rates are reflected from Table 3 because none of the MOEs approach 100. Daily acres treated are based on HED's estimates of acreage that would be reasonably expected to be treated in a single day for each exposure scenario of concern.

[d] Daily Dose (mg/kg/day) = Unit Dose (mg/kg/lb ai) x Appl. Rate (lb ai/A or lb ai/gal) x Amount handled (acres or gallons).

[e] MOE = NOAEL/Daily Dose (mg/kg/day). NOAEL = 0.10 mg/kg/day (oral human toxicity data). MOE of 10 is considered acceptable.

Table E.4. Labels Referenced for Agricultural Use Rate Information

Exposure Scenario (Scenario #)	**Reference Product and EPA Registration No.**
Mixer/Loader Exposure	
Mixing/Loading Liquids for Aerial/Chemigation Application (1a)	Lorsban-4E - 62719-220 Lorsban 4E-SG - 62719-245 Lock-On - 62719 - 079
Mixing/Loading Liquids for Groundboom Application (1b)	Lorsban-4E - 62719-220 Lorsban 4E-SG - 62719-245
Mixing/Loading Liquids for Airblast Application (1c)	Lorsban-4E - 62719-220
Mixing WP for Aerial/Chemigation Application (2a)	Lorsban 50W in Water Soluble Packets - 62719-221
Mixing WP for Groundboom Application (2b)	Lorsban 50W in Water Soluble Packets - 62719-221
Mixing WP for Airblast Application (2c)	Lorsban 50W in Water Soluble Packets - 62719-221
Loading Granulars for Aerial Application (3a)	Lorsban 15G - 62719-034
Loading Granulars for Ground Application (3b)	Lorsban 15G - 62719-034
Mixing Dry Flowables for Aerial/Chemigation Application (4a)	No commercially available products
Mixing Dry Flowables for Groundboom Application (4b)	No commercially available products
Mixing Dry Flowables for Airblast Application (4c)	No commercially available products
Applicator Exposure	
Aerial (Spray) -- Enclosed Cockpit (5a)	Lorsban-4E - 62719-220 Lorsban 4E-SG - 62719-245 Lock-On - 62719 - 079 Lorsban 50W in Water Soluble Packets - 62719-221
Aerial (Granulars) -- Enclosed Cockpit (5b)	Lorsban 15G - 62719-034
Groundboom Tractor (6)	Lorsban-4E - 62719-220 Lorsban 4E-SG - 62719-245 Lorsban 50W in Water Soluble Packets - 62719-221
Airblast Applicator (7)	Lorsban-4E - 62719-220 Lorsban 50W in Water Soluble Packets - 62719-221
Tractor-Drawn Granular Spreader (8)	Lorsban 15G - 62719-034
Seed Treatment (9)	Lorsban 50-SL 62719-038
Dip Application (Preplant Peaches) (10)	Lorsban-4E - 62719-220
Exposure Scenario (Scenario #)	**Reference Product and EPA Registration No.**
Flagger Exposure	
Spray Applications (11)	Lorsban-4E - 62719-220 Lorsban 4E-SG - 62719-245 Lock-On - 62719 - 079 Lorsban 50W in Water Soluble Packets - 62719-221
Granular Applications (12)	Lorsban 15G - 62719-034
Mixer/Loader/Applicator Exposure	
Backpack Sprayer (13)	
Low Pressure Handwand (14)	
High Pressure Handwand (greenhouse uses) (15)	
Hyraulic Hand-held Sprayer for Bark Treatment (16)	Lorsban-4E - 62719-220
Dry Bulk Fertilizer Impregnation	Lorsban-4E - 62719-220

Appendix F: DAS Calculations for Exposure Assessment

Exposure: Inhalation
Application: Post
Receptor: Adult/Child
Method: Air Concentration

Inputs:

Parameter	Use	Application Rate	Adult	Child	Units	Source
Air concentration of AI	Dursban 50W Turf	4 lb/acre	20.50	20.50	ug/m^3	Max. air conc. Vaccaro et al., 1993
	Dursban 50W Turf	1 lb/acre	5.13	5.13		¼ air concentration in Vaccaro et al., 1993
Note For turf assessments Vaccaro et al., 1993 and Vaccaro et al., 1996 air concentrations were used as surrogate data for Stafford et al., 1999 turf dislodgeable study.	Dursban Pro Turf	4 lb/acre	20.5	20.5		Max. air conc. Vaccaro et al., 1993
	Dursban Pro Turf	1 lb/acre	5.13	5.13		¼ air conc. in Vaccaro et al., 1993
	Dursban 2.5G Turf	2 lb/acre	1.06	1.06		Max. conc. Vaccaro et al., 1996
	Dursban 2.5G Turf	1 lb/acre	0.53	0.53		½ max air conc. in Vaccaro et al., 1996
	Dursban Pro C&C	0.5%	2.33	2.33		Max. air conc. Byrne, et al., 1998
	Dursban Pro C&C	0.25%	1.16	1.16		½ max air conc. in Byrne, et al., 1998
	Dursban Termite		0.29	0.29		Max. air conc. Vaccaro et al., 1987
Note: C&C was based on 15" air sampler in kitchen of house #2.						
Exposure Duration	Turf		1.1	2.2	hr/day	AIHC
	C&C/Termite		18.3	19.6		AIHC
Inhalation Rate			0.71	0.47	m^3/hr	REx
Body Weight			70	15	kg	AIHC

Calculation:

$$Exposure = \frac{(Air\ Concentration\ x\ ug/1000mg) \times (InhalationRate) \times (Exp\ Duration)}{(Body\ Weight)}$$

Exposure: Dermal
Application: Post
Receptor: Adult/Child
Method: Transfer Factor (Residue)

Inputs:

Parameter	Use	Rate	Adult	Child	Units	Source
Dislodgeable Residue (Surface)	Dursban 50W Turf	4 lb/acre	6.6×10^{-4}	6.6×10^{-4}	mg/cm^2	Max. conc. Stafford et al., 1999
(Environment/Pet)	Dursban 50W Turf	1 lb/acre	1.65×10^{-4}	1.65×10^{-4}		¼ conc. of Stafford et al., 1999
	Dursban Pro Turf	4 lb/acre	1.5×10^{-4}	1.5×10^{-4}		Max. conc. Stafford et al., 1999
	Dursban Pro Turf	1 lb/acre	3.75×10^{-5}	3.75×10^{-5}		¼ conc. of Stafford et al., 1999
	Dursban 2.5G Turf	2 lb/acre	3.0×10^{-6}	3.0×10^{-6}		LOQ of Stafford et al., 1999
	Dursban 2.5G Turf	1 lb/acre	1.5×10^{-6}	1.5×10^{-6}		½ LOQ of Stafford et al., 1999
Note: Dermal exposure for C&C used 50% of highest deposition pad (day 1) as the dislodgeable residue.	Dursban Pro C&C	0.5%	1.2×10^{-5}	1.2×10^{-5}		Max. conc. Byrne et al., 1998
	Dursban Pro C&C	0.25%	5.8×10^{-6}	5.8×10^{-6}		½ conc. of Byrne et al., 1998
Transfer Factor – Hands (Ucovered)			7.744	7.744	unitless	REx
Transfer Factor – Hands (Covered)			0	0	unitless	REx
Transfer Factor – Upper Body (Uncovered)			2.62	2.62	unitless	REx
Transfer Factor – Upper Body (Covered)			0.026	0.026	unitless	REx
Transfer Factor – Lower Body (Uncovered)			2.938	2.938	unitless	REx
Transfer Factor – Lower Body (Covered)			0.029	0.029	unitless	REx
Transfer Factor – Feet (Uncovered)			18.69	18.69	unitless	REx
Transfer Factor – Feet (Covered)			0	0	unitless	REx
Clothing Penetration Fraction (Uncovered)			1	1	unitless	REx
Clothing Penetration Fraction (Covered)			0.5	0.5	unitless	REx
Reference Duration			1	1	day	REx
Surface Area (Hands) (Uncovered)			793	452	cm^2	REx
Surface Area (Hands) (Covered)			0	0	cm^2	REx
Surface Area (Upper Body) (Uncovered)			2190	1085	cm^2	REx
Surface Area (Upper Body) (Covered)			3705	1615	cm^2	REx
Surface Area (Lower Body) (Uncovered)			3972	1650	cm^2	REx
Surface Area (Lower Body) (Covered)			2845	1220	cm^2	REx
Surface Area (Feet) (Uncovered)			1048	553	cm^2	REx
Surface Area (Feet) (Covered)			0	0	cm^2	REx
Body Weight			70	15	kg	AIHC

Calculation:

$$Exposure = \frac{\sum\{(Trans\ Fact)\times(Surf\ \ Area)\times(Cloth\ \ Factor)\}\times(Dislodge\ \ Re\,s)}{(Re\,f\ \ Duration)\times(Body\ \ Weight)}$$

Exposure: Oral from Grass/Plants
Application: Post
Receptor: Child
Method: Direct: Grass

Inputs:

Parameter	Use	Turf Spray Application Rate (lb/acre)	Units	Source
Application (Area treated)	Dursban 50W Turf Dursban 50W Turf Dursban Pro Turf Dursban Pro Turf Dursban 2.5G Turf Dursban 2.5G Turf	4 1 4 1 2 1	lb/acre	Max. DAS label rate ¼ of Max. DAS label rate Max. DAS label rate ¼ of Max. DAS label rate Max. DAS label rate ½of Max. DAS label rate
Ground Cover (Grass / Plants)		0.01	g/cm^2	REx
Fraction AI Dislodgeable from Grass / Plants		0.02	unitless	Stafford et al., 1999
Fraction AI Dissipated Daily		0.5	unitless	REx
Ingestion Rate (Grass / Plants)		25	cm^2/day	REx
time (= Post Application Day)		0	day	REx
Body Weight		15	kg	AIHC

Calculation:

$$\mathrm{Re}\,sidue_{grass} = \frac{(kg\ ai/m2)\times(Frac\ \ AI\ Grass)\times(1-Frac\ \ Dissipated\ \ Daily)^{t}}{(Ground\ \ Cover)}$$

where: $kg\ ai/m2 = (lb/acre)x(0.45\,kg/lb)/(4048\,m^2/acre)$

$$Exposure = \frac{(Re\,sidue)_{grass}\times(Ingestion\ \ Rate)_{grass}}{(Body\ \ Weight)}$$

Exposure: Oral from Incidental: Hand-To-Mouth Transfer
Application: Post
Receptor: Child
Method: Incidental: Hand-To-Mouth Transfer

Inputs:

Parameter	Units	Use	Application Rate	Residue Concentration	Units	Source
Transferable Residue	mg/cm^2	Dursban 50W Turf	4 lb/acre	6.6×10^{-4}	mg/cm^2	Max. conc. Stafford et al., 1999
		Dursban 50W Turf	1 lb/acre	1.65×10^{-4}		¼ conc. of Stafford et al., 1999
		Dursban Pro Turf	4 lb/acre	1.5×10^{-4}		Max. conc. Stafford et al., 1999
		Dursban Pro Turf	1 lb/acre	3.75×10^{-5}		¼ conc. of Stafford et al., 1999
		Dursban 2.5G Turf	2 lb/acre	3.0×10^{-6}		Max. conc. Stafford et al., 1999
		Dursban 2.5G Turf	1 lb/acre	1.5×10^{-6}		½ conc. of Stafford et al., 1999
		Dursban Pro C&C	0.5%	1.2×10^{-5}		Max. conc. Byrne et al., 1998
		Dursban Pro C&C	0.25%	5.8×10^{-6}		½ conc. of Byrne et al., 1998
Transfer Coefficient	$cm^2/hour$			4500	$cm^2/hour$	EPA
Transfer Factor Hands Uncovered				7.744	unitless	REx
Clothing Penetration Factor Uncovered				1	Unitless	REx
Hand Surface Area				452	cm^2	REx
Fraction Transferred	unitless			0.1	unitless	REx
Reference Duration				1	days	REx
Exposure Duration	hr/day			1	hr/day	REx
Contact Frequency (Hand-To-Mouth)	events/hr			1.56	events/hr	REx
Transfer Efficiency (Hand-To-Mouth)	unitless			0.1	unitless	REx
Exposure Duration (Hand-To-Mouth)	hr			1	hr	REx
Body Weight	kg			15	kg	EPA

Calculation:

$$Transfer\ Factor_{HandToMouth} = (Transfer\ Eff) \times \sum_{n=1}^{[(\text{Contact Freq}) \times (Exp\ Duration)]} [1 - (Transfer\ Eff)]^n$$

$$Hand\ Exposure_{dermal} = \frac{(Dis\log ible\ \text{Re}\ sidue) x (TF\ \ Hands\ x\ CP\ Factor\ x\ Surface\ Area\ Hand)}{\text{Re}\ ference\ Duration}$$

where: TF is Transfer Factor for Hands Uncovered
CP is Clothing Penetration
Calculation is based on uncovered hands

$$Exposure = \frac{(Hand\ Exposure)_{Dermal} \times (Transfer\ Factor)_{HandToMouth}}{(Body\ Weight)} x\ (Fraction\ Absorbed)$$

Appendix G: Pertinent Errors or Misrepresentations Regarding Review by Jerome Blondell Dated February 11, 1999

Page 2, paragraph 3. "*The calls are initially handled by a poison information specialist who has been trained and certified by examination.*"

This statement gives the impression that each individual responding to calls in a PC is trained and certified (CSPI). However, this is not true. While at least *one* CSPI must be on duty at all times in a *certified* PC, the remainder of personnel answering calls need not be certified. In non-certified centers, comprising one-third of all reporting centers, there is no legal obligation that the information specialist has any specific training. Thus, the level of expertise of the information specialist varies significantly from one center to the next, even in certified centers. This does not, *per se*, indicate a data quality issue as many calls are requests for information or relate to non-toxic exposures, which may be safely handled by non-certified personnel with limited training. However, there is no assurance that these same personnel are not taking significant exposure calls in some centers, and it is clear that the judgment of association or "causation" depends on familiarity with the product and/or product family in question. This knowledge varies with training (physician, clinical pharmacist, registered nurse, nursing or pharmacy student, emergency medical technician) and experience. Thus, the attribution of "causation" by PC personnel must take into consideration this variability in training and certification as well as the inherent limitations in telephone based reporting.

Page 3, paragraph 1. "*When symptoms or signs occur they are categorized into minor, moderate, or major depending on their severity and whether recovery is complete.*"

This categorization deserves further comment, specifically with regard to odor-mediated complaints. Any categorization of complaints is subject to limitations. While the AAPCC definitions are generally functional, some symptoms are not easily classified between minor and moderate. For example, if a chemical or its carrier solvent has an unpleasant odor which is not rapidly dissipated (minutes to hours), each "exposure" to that product may produce reactions not necessarily of a toxic nature. Most individuals have some visceral reaction to the smell of vomitus, a dead animal, or a rotten egg. The range of symptoms between individuals varies from

none at all, to nausea, headache, fainting, etc. Repeated or persistent reactions to such an odor may be interpreted as "prolonged" by the information specialist, leading to a moderate classification. While the symptoms may, in fact, be moderate, the underlying toxicity may be minimal or non-existent. Thus, the occurrence of moderate symptoms cannot be ascribed *stricto senso* to the inherent toxicity of the product.

Page 3, last paragraph. "*Cases were reviewed to determine how accurately the information coded in TESS matched the information in the original medical record.*"

This statement gives the impression that actual patient medical records (as opposed to PC documentation) were reviewed. The PC record is the documentation of a telephonic interview between an information specialist, who may or may not be a licensed health care provider, and a caller who may or may not be the "patient." The patient, in general, is not known to the specialist in the sense of an established "provider-patient relationship." While AAPCC requires this document be "acceptable as a medical record," whether it actually is, from a legal standpoint, is debatable. In any case, it cannot substitute for the kind of record that results from direct face-to-face patient contact. Thus, this statement should be modified to indicate "original poison center

Substance was correctly coded 93.3% of the time, incorrectly coded 6.5%, and unable to determine if correct 0.2%."

It is disturbing that miscoding of the substance during the transfer from the PC record to the TESS data collection form occurs at a rate of approximately 7%. One must also keep in mind that the *original* identification of the compound in question is dependent on the willingness and ability of the caller to correctly identify the chemical, and on the tenacity of the information specialist for exacting important details (EPA registration numbers, bar codes, product numbers, none of which are part of the TESS data collection form). This, too, may result in magnification of this important error. Also, note that no quality audit of the fields of "clinical effects," "duration of symptoms," or "treatment rendered" were performed. The first two of these fields were cited

frequently and the third contains information that may have been useful in examining cases regarding “hospitalized” patients.

Page 5, paragraph 3. “*Poison specialists must rely on their experience and judgment to determine which cases have symptoms consistent with the toxicology, dose, and timing of the exposure. While some misclassification can be expected to occur from this approach, it is not expected to be differentially biased among pesticides. That is, there is no reason to believe that Poison Specialists are likely to misclassify one organophosphate more or less than another.*”

The first sentence is true and, as has been pointed out, this experience and judgment may vary tremendously. The second sentence is wrong unless one adds “of the same class” to the end of it. While one would not anticipate misclassification, perhaps, between two pyrethroids, the likelihood of associating a symptom to an organophosphate is much greater because the organophosphate symptom complex (toxidrome) involves the entire parasympathetic nervous system. In other words, the symptoms known to be associated with pyrethroids (dysesthesias, allergy, asthma) are much more specific than those associated with organophosphates (headache, nausea, diarrhea). Thus, common illnesses, such as headache, viral enteritis, food-borne illness, and influenza are much more likely to be inaccurately attributed to an organophosphate in the absence of corroborating evidence of exposure.

Page 6, Table 1. Organophosphates not identified.

In more than one-third of the cases, the organophosphate involved could not be identified by name. This raises additional questions about the quality of this data. How does one attribute reported symptoms to “organophosphate, not identified?” What is the accuracy of such identification?

Page 7, last paragraph. “*Children under age six accounted for 40% of all organophosphate exposures and more than half of the exposures to chlorpyrifos (51%), naled (60%) and tetrachlorvinphos.*”

The significance of this statement is unclear. It is a well-known fact the majority of accidental exposures to all household products and pharmaceuticals occur in children under the age of six years. There is nothing in this statement that speaks to the particular toxicity of organophosphates, in general, or of chlorpyrifos, in particular.

Page 8, paragraph 1. "*Typically, cases are not admitted unless the attending physician feels the case is likely to require extensive treatment to prevent further adverse effects.*"

There is no factual basis whatsoever to this statement, and certainly nothing in the TESS database which permits one to derive such a statement. The *potential* for a serious outcome after suspected or reported organophosphate ingestion, in the absence of any signs or symptoms, may be sufficient in the mind of a physician to require admission to the hospital for observation. Children, more commonly than adults, vomit after chemical or drug ingestion, regardless of toxicity. Given that vomiting is one of the many non-specific signs of organophosphate poisoning, it might be anticipated, on the contrary, that physicians would admit the *majority* of "symptomatic" suspected organophosphate ingestions, without regard to concerns for the need for "extensive treatment." In fact, Table 3 suggests this is true, as only 19.9% of chlorpyrifos ingestions presenting to a health care facility (HCF) were symptomatic and two-thirds of those (12.6% of patients seen) were admitted. The conservative physician, understanding the limitations of hospital care on the general ward, might even admit a mildly symptomatic child (nausea and vomiting) to the intensive care unit to avoid any potential for inadequate treatment. A much better measure of "requirement for extensive treatment" would be the use of specific antidotes or endotracheal intubation, both of which are "treatment" data fields that have been omitted from the analysis.

Page 8, paragraph 3. "*A primary measure of hazard is the incident rate defined as the number of individuals who became ill divided by the number at risk over some time period.*"

This is an accurate statement. Table 6, however, provides no information about the number of major or fatal cases per million containers or applications, which many would consider a more

useful estimate of true risk associated with a product than the simple occurrence of potentially consistent symptoms. Using the numbers from Table 2 (8998 exposures/4 years for chlorpyrifos) and Table 3 (19.9% symptomatic, 0.3% major or fatal), one arrives at the following figures. Average annual exposures for children under age 6 = 8998/4 = 2250. If 19.9% are symptomatic, one arrives at a figure of 448/year. If this represents 12.9 cases per million containers or 1.0 cases per million applications, one arrives at figures of 34,709,302 containers and 448 million applications. Thus, the number of major or fatal cases per million containers is approximately 0.19 and the number of such cases per million applications is 0.015. In other words, this represents 0.00015 major or fatal cases per 10,000 applications.

Page 9, last paragraph. "*These data strongly support the finding that organophosphates pose a much greater risk of severe poisoning in young children than do other pesticides.*"

While it cannot be denied that organophosphates are more toxic than boric acid, piperonyl butoxide, pyrethrins, and insect repellants, the comparison is not compelling. Organophosphate pesticides are intended for use against resistant pests, like termites and ants. It stands to reason they should be inherently more toxic than a product which one applies to the skin to repel mosquitoes. A more realistic comparison is against products with similar use patterns, such as the organochlorines, which organophosphates have largely replaced, and the carbamates.

Page 11, last paragraph. "*For children under age six, they are over five times more likely to be admitted to an ICU if exposed to an organophosphate pesticide.*"

Once again, it cannot be denied that organophosphates are more toxic, in general, than pyrethrins, boric acid, and some other pesticides. <u>However, it must be stressed again that the statements about hospitalization and ICU admission are based on figures without an accurate denominator</u>. If health care providers are less likely than the public to call a PC for advice, they are more likely to call when they perceive a higher potential risk. For example, a physician might choose not to call a PC about a pyrethroid exposure, because he/she is confident it is nontoxic. That same physician might choose to admit an asymptomatic child having ingested an organophosphate to

the intensive care unit as a precaution and to call the PC because he realizes the *potential* for toxicity is greater. The final outcome for both children may be identical. Such habits would tend to exaggerate the hospitalization/ICU admission rates for certain compounds relative to others. The PC consultation habits of physicians remain largely unknown, so analysis of these data must be extremely guarded.

Page 17, last paragraph. *"For organophosphate cases with a moderate, major or fatal outcome, one-quarter of them are due to environmental exposures. Especially high in this category were acephate, propetamphos, and chlorpyrifos."*

This statement is misleading by its broad categorical grouping. In the four years studied, not one death was reported due to environmental exposure to chlorpyrifos. The total number of major cases attributable to environmental exposure to chlorpyrifos during the study period was substantially less than 1%. Thus, 175 of these "moderate, major, or fatal outcomes" are in the moderate category as noted in appendix Table 4. The pitfalls of this categorical system have been discussed, but it is worth repeating that if an unpleasant odor results in nausea, vomiting, lightheadedness, or malaise on and off for two to three days, this is likely to be coded as a moderate outcome, even if the symptoms are in no way related to actual toxicity of the product itself, but rather to odor-mediated phenomena.

Page 18, last paragraph. *"A detailed examination of the 120 chlorpyrifos cases with persistent effects found 41% were due to environmental exposures, 90% were adults or older children (6-19 years old), 63% were women, and the most common symptom category was neurological, also consistent with earlier reports."*

This statement reflects the limited likelihood of a toxicological relationship of chlorpyrifos to persistent effects. If the persistent effects were of an objective nature (such as vomiting, diarrhea, sweating) rather than subjective (such as nausea or headache), one would expect younger children to have greater persistent symptoms than adults.

Although TESS data categorizes signs and symptoms by "organ" system for simplicity sake, it is impossible to determine whether a "neurological" sign or symptom reported over the telephone is of an organic or functional etiology. Thus, a stress induced tension headache is indistinguishable from a headache from carbon monoxide poisoning.

This statement also points out that a majority of the persistently ill are women, a fact that might be attributed to the greater percentage of poison exposure cases involving female patients as represented in the TESS database.

In fact, the persistent symptoms most often reported by Blondell and Dobozy (persistent headaches, blurred vision, muscle weakness, and problems with memory, concentration, confusion, depression, and irritability) after organophosphate environmental exposures are remarkably similar to those of MCS. The American Medical Association (AMA 1992) has said of MCS in a position paper, "The constellation of symptoms presented (e.g., depression, fatigue, irritability, difficulty in breathing, headache, gastrointestinal distress, and food intolerance) resemble those seen in many illnesses." They go on to say, "…no scientific evidence supports the contention that MCSS is a significant cause of disease…" and that "…the American Medical Association Council on Scientific Affairs believes that multiple chemical sensitivity should not be considered a recognized clinical syndrome."

Moreover, one of the most recent studies conducted on patients alleging MCS involved a retrospective review and classification of sixty-one (61) MCS patients seen over a ten-year period. The authors concluded that MCS is best characterized as a manifestation of one of several primary psychiatric disorders. Witorsch, P., Ayesu K., Balter, N.J., Schwartz, S.L., "Multiple Chemical Sensitivity: Clinical Features and Causal Analysis in Sixty-One (61) Cases," *Journal Clin. Toxicol.*, **33**:524-525, 1995.

Finally, numerous published studies also confirm that the typical constellation of MCS symptoms ha a psychogenic basis, including Black, D.W., "Iatrogenic (physician-induced) hypochondriasis,

Four patient examples of "Chemical Sensitivity," Psychosomatics 37:390:393 (1996); Black, D.W., Psychiatric perspective of persons with "Environmental Illness," Clin. Rev. Allergy Immunol., 14:337-355 (1996); Black, D.W., Rathe, A., Goldstein, R.B., "Environmental Illness. A controlled study of 26 subjects with '20th Century Disease,'" JAMA 264:3166-3170 (1990); Simon GE. Daniel W. Stockbridge H, Claypoole K, Rosenstock L, "Immunologic, psychological, and neuropsychological factors in multiple chemical sensitivity," Ann Intern Med 119:97-103 (1993); Simon GE, "Psychiatric symptoms in multiple chemical sensitivity, " Toxicol Ind Health 10:487-496 (1994); Terr, Abba, "Clinical Ecology in the Workplace," Journal of Occupational Medicine, Vol. 31, pp. 257-61 (March 1989); Staudenmeyer, Herman, e al., "Adult Sequelae of Childhood Abuse Presenting As Environmental Illness," Annals Allergy, Vol, 71, No. 6 (Dec. 1993).

It is imperative that one separate those symptoms resulting from demonstrable cholinesterase deficiency secondary to acute organophosphate poisoning as compared to those from undocumented environmental exposure. Patients suffering acute significant poisoning have demonstrated objective findings of neurological injury.

Page 27, paragraph 1. "*One crude way to get an idea of the hazard from a particular organophosphate is to tally the number of times it ranks in the top 3 for Tables 3-8, excluding those measure that were unreliable due to small sample size.*"

One would have to agree with EPA this is a crude means to judge a hazard. The tables are based on voluntary reporting to PCs, 100% of which is done over the telephone, 87% of which is reported by non-medical personnel, without the benefit of direct physical examination, or in most cases, corroborating evidence, such as measurement of ChE enzymes. The determination of "relatedness" of symptoms is performed by an information specialist who may or may not be a certified or licensed health care professional, and who is unlikely to have professional training in industrial hygiene, indispensable to the evaluation of environmental toxicity. The data has no known denominator (number of calls versus the actual incidence of exposures and/or toxic effects), and is subject to both over reporting (concerned parents) and under reporting

(knowledgeable physicians). Hamilton and Goldfrank have recently adeptly addressed the pitfalls of over-analyzing PC data.

The data are not, however, without merit. They demonstrate the vast majority of reported exposures to organophosphates, for whom outcome is recorded, result in no or minor symptoms. They do indicate that organophosphates can result in serious or lethal toxicity, but the incidence of these, in relation to their widespread use, is moderate. DAS shares concern for public health and supports efforts to diminish even these small numbers where reasonably possible.

Appendix H: Listing of Published Papers Supporting Reregistration of Chlorpyrifos

H.1. FQPA: Safety Factors

Gibson, J. E., "Implications of the Food Quality Protection Act for Pesticide Residue Tolerances: Organophosphates," 1998. ***Toxicology Forum, Annual Summer Meeting (July): 483-493.***

> FQPA implementation has become a complex subject. This paper discusses issues associated with application of the additional 10X safety factor and both aggregate and acute dietary risk assessments using chlorpyrifos as a case study. Implementation of FQPA will require adoption of new methods and processes and must also incorporate sound science, transparency of process, balance and workability.

Carlock L, Chen WL, Gordon E, Kileen J, Manley A, Meyer L, Mullin L, Pendino K, Percy A, Sargent D, Seaman L, Svanbory NK, Stanton R, Tellone C, Van Goethem D. 1999-*In press*. Regulating and assessing risks of cholinesterase-inhibiting pesticides: Divergent approaches and interpretations. ***Journal of Toxicology and Environmental Health, Part B, 2:105-160.***

> This document presents a revised framework for conducting worker and dietary risk assessments for less-than-lifetime exposures to organophosphate or carbamate pesticides based on RBC or brain AChE inhibition or the presence of clinical signs and symptoms. The proposals for appropriate UFs are based on the biological significance of the ChE inhibition noted at the LOEL and the degree of uncertainty in the extrapolation between human and animal data. These conclusions are based on an extensive evaluation of industry guideline studies and the available published literature

Gibson JE, Chen WL, Peterson RKD. 1999. How to determine if an additional 10x safety factor is needed for chemicals: A case study with chlorpyrifos. ***Toxicological Sciences, 48: 117-122*****.**

> The SAP has established a 5-step process (based on the risk assessment paradigm) to determine the need for, or against, an "additional" 10X safety factor. This approach takes all of the available toxicity and exposure information for a chemical into account rather than focusing on only selected considerations of identified potential hazards. Using chlorpyrifos as a case study, we have demonstrated how scientific evidence of toxicity and exposure can, and should, be used in the FQPA

safety factor decision process. When the SAP's scientific weight of evidence approach is applied to chlorpyrifos, it is evident that the additional 10X safety factor for children is not needed.

Schardein JL, Scialli AR. 1999. The legislation of toxicologic safety factors: the Food Quality Protection Act with chlorpyrifos as a test case. *Reproductive Toxicology Journal 13(1): 1-14*.

Adequate protection of the public is afforded by the current reference doses. There is no scientific rationale for the application of an additional uncertainty factor to chlorpyrifos under the FQPA.

H.2. FQPA: Developmental Neurotox: Lack of Differential Sensitivity

Maurissen JPJ, Hoberman AM, Garman RH, Hanley TR, Jr. 1998-*Submitted for publication*. Lack of developmental neurotoxicily in rat pups from dams treated by gavage with chlorpyrifos. *Toxico. Sci.*

Pregnant Sprague Dawley rats were given chlorpyrifos by gavage from gestation day 6 (GD 6) through postnatal day 10 (PND 10) at dosages of 0, 0.3, 1 or 5 mg/kg/day in a developmental neurotoxicity study that conformed to EPA's 1991 guidelines. Toxicity was limited to the highest dosage level (5 mg/kg/day). Although all reproduction indices were normal, pups from high-dosage dams had increased mortality soon after birth, gained weight more slowly than controls, and had several indications of slightly delayed maturation. The early deaths and delayed maturation were attributed to maternal neglect secondary to maternal toxicity. No effects were noted in either dams or pups at 1 or 0.3 mg/kg/day. Based on these data, there was no evidence of selective developmental neurotoxicity following exposure to chlorpyrifos even at a dose level which produced obvious maternal toxicity.

Mattson JL, Maurissen JP, Nolan RJ, Brzak KA. 1998-*Submitted for publication*. Lack of differential sensitivity to cholinesterase inhibition in fetuses and neonates compared to dams treated perinatally with chlorpyrifos. *Toxicol. Sci.*

Pregnant Sprague Dawley rats were exposed to chlorpyrifos by gavage from gestation day (GD) 6 to postnatal day (PND) 10. Dosages to the dams were 0, 0.3, 1.0 or 5.0 mg/kg/day. On GD 20, the blood CPF concentration in fetuses was about one-half to one-third the level found in their dams. Based on blood chlorpyrifos levels, pups were more tolerant to ChE inhibition than were dams at these dosage levels. Inhibition of ChE occurred at all dosage levels in dams, but

only at the high-dosage level in pups. At the high dosage, ChE inhibition was greater in dams than in pups, and the relative degree of inhibition was RBC≈plasma≥heart>brain (least inhibited). ChE levels of all tissues of high-dosage pups rapidly return to near control levels by PND 5, further indicating a lack of differential sensitivity at this dosage level.

H.3. Toxicology: Exposure and Human Health

Kingston RL, Chen WL, Borron SW, Sioris LJ, Harris CR, Engebretsen KM. March, 1999-*In press*. Chlorpyrifos: Ten year U.S. poison center exposure experience. *Veterinary and Human Toxicology, 41 (2)(April): 87-92.*

An analysis of the poison center data showed that chlorpyrifos-containing products have an acceptable and safe profile. For example, chlorpyrifos received about the same number of calls as household bleach. There were fewer than six calls requiring medical attention per million pounds of chlorpyrifos sold.

Clegg DJ, Van Gemert M. 1999-*In press*. Expert panel of human case studies on chlorpyrifos and/or other organophosphate exposures. *Journal of Toxicology and Environmental Health.*

A panel of toxicology and medical experts was convened on April 7-9, 1997 to consider the available scientific literature on chlorpyrifos. Members of the expert panel were:

James W. Albers, M.D., Ph.D., Department of Neurology, University of Michigan
David J. Clegg, M.Sc., Formerly, Head of Pesticide Toxicology, Health Canada
Philip S. Guzelian, M.D., Department of Medicine, University of Colorado
Marcello Lotti, M.D., Istituto di Medicina del Lavoro, Universita di Padova
Rudy J. Richardson, Sc.D., Toxicology Program, University of Michigan
Mike Watson, M.Sc., Formerly, Head of Toxicology, Pesticide Safety Directorate, UK

The expert panel concluded:

- For acute poisonings there was no clear evidence for long-term effects from organophosphates, other than finding cases of OPIDN from suicidal ingestion.
- Long-term exposure to organophosphate compounds does not cause problems in the peripheral or central nervous system, unless poisoning is acute and severe.
- Manifestations of clinical neurobehavioral effects are unlikely.
- All of the available evidence shows that toxicological effects do not occur unless AChE inhibition has been clearly exhibited.

Shackelford DD, Young DL, Mihaliak CA, Shurdut BA, Itak JA. 1999. A practical immunochemical method for determination of 3,5,6-trichloro-2-pyridinol in human urine: Applications and considerations for exposure assessment. *J. Agric. Food Chem, 47: 177-182.*

This paper describes a new immunochemical analytical method for the rapid quantitative determination of 3,5,6-TCP in human urine resulting from chlorpyrifos, chlorpyrifos-methyl, or triclopyr exposure. Appropriate methodology for calculating chlorpyrifos equivalent doses from the concentrations of 3,5,6-TCP in the urine using PK data is described.

Albers JW, Cole P, Greenberg RS, Mandel JS, Monson RR, Ross JH, Spurgeon A, Van Gemert M. 1999. Analysis of chlorpyrifos exposure and human health: Expert panel report, 1998. *Journal of Toxicology and Environmental Health, Part B, 2(4): 101-124.*

An epidemiology panel composed of international health experts concluded that chlorpyrifos had not been shown to be a concern for public health after examining the relevant data. The Panel examined available scientific evidence on a variety of neurological, behavioral and immunological disorders, multiple complaints (often called MCS) and birth defects. After extensive review, the Panel was not persuaded that exposure to chlorpyrifos containing products caused any of these conditions in humans. The panel's report was submitted to EPA on October 20, 1997.

H.4. Toxicology: Reference Dose

Chen WL, Sheets JJ, Nolan RJ, Mattsson JL. February, 1999. Human red blood cell acetylcholinesterase inhibition as the appropriate and conservative surrogate endpoint for establishing chlorpyrifos reference dose. *Regulatory Toxicology and Pharmacology, 29:15-22*.

Currently, the RfD used by the EPA to establish acceptable human exposure tolerances for chlorpyrifos is based upon inhibition of plasma BuChE, which is not the target enzyme of chlorpyrifos, and does not play any role in cholinergic transmission. Data are presented showing that inhibition of AChE associated with RBC, an enzyme similar to or identical with that in the nervous system, is a more appropriate and still conservative endpoint on which to base the RfD. Chlorpyrifos RfD based on inhibition of RBC AChE activity is protective of both adults and infants.

Clegg DJ, Van Gemert M. 1999-*In press*. Determination of the reference dose for chlorpyrifos: Proceeding of an expert panel. *Journal of Toxicology and Environmental Health.*

In April 1997 an independent expert panel was convened to review and evaluate all relevant documents with respect to the determination of RfDs for chlorpyrifos. Members of the expert panel were:

James W. Albers, M.D., Ph.D., Department of Neurology, University of Michigan
David J. Clegg, M.Sc., Formerly, Head of Pesticide Toxicology, Health Canada
Philip S. Guzelian, M.D., Department of Medicine, University of Colorado
Marcello Lotti, M.D., Istituto di Medicina del Lavoro, Universita di Padova
Rudy J. Richardson, Sc.D., Toxicology Program, University of Michigan
Mike Watson, M.Sc., Formerly, Head of Toxicology, Pesticide Safety Directorate, UK

After a thorough review and evaluation of all the animal and human data, the independent expert panel concluded that human plasma butrylcholinesterase should not be used for setting RfDs. Acute and chronic RfD values for chlorpyrifos of 0.05 mg/kg and 0.01 mg/kg/day, respectively (based on NOELs of human RBC or animal brain acetylcholinesterase inhibition) are sufficient to protect adults as well as infants and children.

H.5. Risk Assessment: Aggregate

Shurdut BA, Barraj L, Francis M. December, 1998. Aggregate exposures under the Food Quality Protection Act: An approach using chlorpyrifos. *Reg. Tox. & Pharm., 28: 165-177.*

This paper describes a state-of-the-art methodology to characterize potential aggregate exposures to chlorpyrifos by assimilating information regarding typical use patterns, as well as quantitative exposure and dose measurements. Studies measuring 3,5,6-trichloropyridinol, the primary metabolite of chlorpyrifos, in the urine of individuals living in the U.S. show that aggregate exposures derived from this approach are consistent with actual population-based measurements and well below relevant toxicological endpoints.

Oliver GR, Bolles HG, Shurdut BA. 1999-*In press*. Chlorpyrifos: Probabilistic Assessment of Exposure and Risk. *NeuroToxicology, 20(1), 000-000*.

Levels of refinement in the both dietary and non-dietary estimated exposure and risk for chlorpyrifos which can be obtained through the use of more relevant exposure data, recognition of patterns of uses and exposures, and higher-tier probabilistic methodologies are shown. Results show a 7- to 26-fold decrease in estimated acute dietary risk and a 30-

to 80-fold decrease in estimated aggregate risk. These decreases are critical for decision-making, since these changes in results also change the conclusions about risk and indicate the levels are within acceptable limits.

H.6. Exposure and Risk Assessment: Dietary

Bolles HG, Dixon-White HE, Peterson RKD, Tomerlin JR, Day EW, Oliver GR. 1999. A US market basket study to determine residues of the insecticide chlorpyrifos. ***Journal of Food and Agricultural Chemistry, Vol. 47, No. 5***

A market basket survey collected 1500 samples of food items that were high impact dietary items in the diets of infants and children: apples, applesauce, apple juice, orange juice, tomatoes, peanut butter, ground beef, pork sausage, and whole milk. All residues of chlorpyrifos were below tolerance values and most were below the LOQ (level at which a scientist can confidently quantify residue).

Bolles HG, Wright JP, Keeler LC, Shaw MC, Oliver GR. 1998-*Prepared for publication.* Tiered acute dietary exposure of pesticides-a consideration of current practice and opportunities for refinement. ***Environmental Health Perspectives.***

Dietary exposure to chlorpyrifos is well understood. A comprehensive pesticide residue database enables review of dietary exposure at the most refined levels. Based on results of the analysis using USDA monitoring data, chlorpyrifos market basket data, and Monte Carlo techniques, levels of acute dietary exposure are within acceptable limits.

H.7. Exposure and Risk Assessment: Non-Dietary

Byrne SL, Shurdut BA, Saunders, DG. 1998. Potential chlorpyrifos exposure to residents following standard crack and crevice treatment. ***Env. Health Perspect., 106:11, 725-731. (online: http://ehpnet1.niehs.nih.gov/docs/1998/106p725-731byrne/abstract)***

Multipathway exposures were evaluated for residents following a crack and crevice application of a chlorpyrifos-based formulation. Potential respiratory, oral, and dermal exposures were evaluated for children. In addition, urine samples were collected from adults and analyzed for the primary metabolite of chlorpyrifos, 3,5,6-trichloropyridinol, to determine total absorbed dose. Estimated exposures to children were less than 2.1 % of the no observed effect level, whereas adults did not have any detectable exposure from the application.

Gibson JE, Peterson RKD, Shurdut BA. 1998. Human exposure and risk from indoor use of chlorpyrifos. ***Environmental Health Perspectives 106:303-306.***

The article discusses the risk from indoor use of chlorpyrifos in juxtaposition with two recent articles published in Environmental Health Perspectives concerning potential exposures to children. The article reviews both toxicity and exposure to chlorpyrifos and concludes that the weight of empirical evidence indicates that the risk of adults or children experiencing an adverse health effect from exposure to chlorpyrifos through both non-dietary and dietary sources is negligible.

Shurdut BA, Vaccaro JR, Nolan RJ. 1998-*Submitted for publication*. Potential chlorpyrifos exposure to residents following turf treatment with a granular pesticide. *Arch. Env. Contam. Toxicol.*

Exposures and risks to residents re-entering recently treated turf are discussed in this paper. An integrated exposure assessment methodology utilizing biological monitoring and passive dosimetry was employed to characterize the magnitude and duration of potential exposures to adults and children. The results indicate potential exposures to both sub-populations were transient and well below conservative toxicological criteria.

Vaccaro JR. 1993. Risks associated with exposure to chlorpyrifos and chlorpyrifos formulation components. *Pesticides in Urban Environments: Fate and Significance (Racke KD, Leslie AR, eds). American Chemical Society, Symposium Series 522.* Washington, DC. *American Chemical Society; 297-306.*

This paper presents a survey of existing exposure studies completed (as of 1993) for a number chlorpyrifos use patterns. Chlorpyrifos is one of the most widely studied pesticides within the research community. Numerous exposure assessments have been conducted by both DAS and academia over the last 20 years. Based on these studies, chlorpyrifos exposures are well characterized and well below relevant toxicological and health guidelines.

Vaccaro JR, Nolan RJ, Murphy PG, Berbrich DB. 1996. The use of a unique study design to estimate exposure to adults and children to surface and airborne chemicals. *American Society of Testing Materials, ASTM STP 1287, 166-183.*

This paper describes an exposure assessment method for the evaluation of potential residential exposures to turf chemicals. An evaluation of re-entry exposures to adults and children was conducted following the application of a liquid based chlorpyrifos formulation. The development and use of such a “state of the art’

multi-pronged assessment strategy represents the most comprehensive attempt to evaluate lawn chemical exposures to children.

H.8. Risk Assessment: Ecological

Giesy JP, Solomon KR, Coats JR, Dixon KR, Giddings JM, Kenaga EE. 1999. Chlorpyrifos: Ecological Risk Assessment in North American Aquatic Environments. *Rev. Environ. Contam. Toxicol. 160:1-129*.

This risk assessment utilized laboratory toxicity data, surface water monitoring data, and information from microcosm and mesocosm studies to develop a probabilistic assessment of the risk of adverse aquatic ecological effects for all chlorpyrifos use patterns in the continental U.S. All lines of evidence suggest that significant disruptions of aquatic ecosystems are not probable, except for a few locations, where site-specific assessments were recommended to refine the risk estimates.

Havens PL, Cryer SA, Rolston LJ. 1998. A Tiered Aquatic Risk Refinement: Case Study -- At-Plant Applications of Granular Chlorpyrifos to Corn. *Env. Toxicol. Chem. 17: 1313-1322*.

This paper describes a tiered assessment process for estimating and refining risks to aquatic organisms from runoff. As a case study, the granular application of chlorpyrifos to corn (Lorsban 15G granular insecticide) was examined with a progression of low-tier screening to higher-tier, geographically-based, assessments tools. The potential effectiveness of various mitigation practices was also simulated. Based on 90th percentile toxicology and exposure endpoints, a two to 16-fold reduction in potential risk was simulated with the refinement process. The results also located localized areas were more product stewardship, user education, potential field research, or more refined assessments may be beneficial. The refined simulation results are briefly compared to field monitoring results and shown to still be conservative.

Poletika NN, Havens PL, Robb CK, Smith RD. *In press*. Organophosphorous insecticide concentration patterns in an agriculturally dominated tributary of the San Joaquin River. *Chapter in ACS Symposium Series: Agrochemical movement: perspective and scale.* ACS Meeting, March 30-31, 1998, Dallas, TX.

This book chapter presents a preliminary exposure assessment for a year-long monitoring project involving movement of chlorpyrifos and other OP insecticides from treated fields into an agriculturally dominated stream. Emphasis is on

methodology developed to infer movement of chemical from publicly available pesticide use reports, using chemical monitoring data and Geographic Information Systems.

H.9. Risk Assessment: Interpreting the Results

Oliver GR. 1999. Is the use of 99.9th percentile for regulatory decision-making under FQPA sound science? *Risk Policy Report, 16 (4)(April): 32-34.*

An examination of the issues supported by our work with chlorpyrifos raise serious doubts that using the 99.9th percentile as a single point to assess acute dietary risk meets the criteria for sound science. The determination of exposures at this extreme percentile has fundamental flaws which are too extensive to be corrected by merely removing one or a few consumption outliers as now being proposed by EPA. The use of a range around the 95th to 97.5th percentiles may be more scientifically reasonable. Some have claimed that at the 99.9th percentile as many as 23,000 children per day may still be exposed to pesticide levels above the regulatory threshold, but our work shows this remaining 0.1% represents combinations of numbers with little resemblance to the real world.

Wolt JD. 1999-*In press*. Exposure endpoint selection in acute dietary risk assessment. *Reg Toxicology and Pharmacology*.

Risk managers (and the public at large) are poorly served when the highly uncertain 99.9th percentile of Monte Carlo analysis is used as the endpoint for regulatory decision-making in acute dietary risk assessment. Regulators are currently using as an interim exposure endpoint the 99.9th percentile of the exposure distribution. This overly conservative endpoint when coupled with already conservative assumptions for toxic effect and uncertainty factors results in risk management decision-making based on a less than one-in-one-million occurrence. Limitations in exposure and consumption data and their interpretation are compounded when risk assessors use only the 99.9th percentile and fail to provide risk managers with assessments utilizing the full richness of analysis available from Monte Carlo analysis.

Spencer PJ, Mattsson JL. 1998-*Submitted for publication*. Protected Potatoes Are Safer Potatoes! *NeuroToxicology*.

EPA is currently proposing to use the 99.9th percentle of the exposure distribution as a single point for regulatory decision-making in acute dietary risk assessments. Using this conservative endpoint and the same assessment approaches being used for pesticides, this paper assesses the degree of exposure to a natural pesticide-

type compound (potato glycoalkaloid) which is found naturally-occurring in potatoes, a very common item in children's diets. At 99.9th percentile, the predicted exposures for children and infants greatly exceed the known effective level for these toxins. Since this the prediction from this assessment that a significant number of children and infants would be severely ill or even dying from eating potatoes conflicts with our common sense reality based on everyday experience, the validity and credibility of this extreme percentile endpoint as a regulatory decision-point is highly questionable. The importance of this point is discussed in the context of the fact that these natural pesticides have functions similar to synthetic pesticides, are more toxic than synthetic pesticides and are present in our diets in substantially higher concentrations than their synthetic counterparts.

H.10. Risk Assessment: General Topics

Peterson RKD, Shurdut BA. 1999-*In Press*. Cockroaches, cockroach management, and human health: A risk analysis approach. *American Entomologist.*

This paper discusses issues related to risks associated with managing cockroaches and the risks associated with not managing cockroaches. Pesticides, such as chlorpyrifos, used in indoor urban environment play a critical role in the control of pests which pose a significant public health risk. When viewed in light of the relatively small risk posed by exposure to these pesticides, the benefits of urban pesticide use are substantial.

Appendix I: Symposium Summary

CHLORPYRIFOS AND HUMAN HEALTH DATA
CONSIDERATIONS UNDER FQPA
October 20-21, 1998

Symposium Summary

Introduction

Robert Scheuplein, Ph.D.
The Weinberg Group, Inc.

The objective of this two-day conference is to explore the future of chlorpyrifos with regard to the regulatory landscape under the Food Quality Protection Act (FQPA) of 1996. The speakers are charged with detailing the experimental data and information that are critical to regulatory decision making for this important compound.

FQPA represents a compromise with environmentalists who were willing to exchange the pesticide regulation method of the Delaney clause – a law passed in 1950 that bans adding carcinogens, as defined by animal ingestion studies, to the diet -- for new language that focuses on protection for children. FQPA substitutes the risk/benefit methodology that formerly regulated these pesticides for the Food and Drug Administration's standard of "reasonable certainty of no harm." This means that there is reasonable certainty that no harm will result from aggregate exposures to pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there are reliable information.

Section 408 2(c) of FQPA authorizes the application of the "tenfold safety factor" to chronic effects of pesticides. The statute presumes that the data have flaws, so a tenfold safety factor must be applied unless it can be shown by some other means (i.e., a two-generation reproduction and developmental study) that the tolerance is safe.

General Overview of Chlorpyrifos

Jim Gibson, Ph.D.
Dow AgroSciences, LLC

The Food Quality Protection Act (FQPA) fundamentally changed the way pesticides are regulated. FQPA set a single, health-based standard for all pesticide residues in food; specified that residues must be deemed "safe" (having a reasonable certainty that no harm will result from aggregate exposures); and required reassessment of all pesticide residues.

Chlorpyrifos has been used for agricultural and urban pest control over the last 30 years. It is the most widely applied organophosphate insecticide, with registrations in over 88 countries. It is used on crops – with 64 approved agricultural uses in the US – as well as in many noncrop (residential/home) situations. It is a broad-spectrum material that controls nearly all economically important pests.

Its worldwide registrations are supported by an extensive proprietary and published database. Chlorpyrifos is the most thoroughly tested pesticide, with over 3,600 studies and nearly 12,000 published citations, including data reviews of its environmental fate, ecotoxicology, neurotoxicity, and dietary risk, plus expert panel reviews assessing the compound's human health and ecological risks.

Much is known about the compound's environmental fate: toxicology studies have been completed on acute exposure, genotoxicity, development, reproduction, subacute exposure, subchronic exposure, and chronic exposure. Chlorpyrifos is rapidly metabolized and excreted as a TCP (trichloropyridinol) metabolite; it does not accumulate in the body. The most sensitive known endpoint of exposure for humans is inhibition of plasma cholinesterase. The NOEL (no observable effect level) for chlorpyrifos is 30 micrograms per kilogram of body weight per day for chronic exposures, 100 micrograms per kilogram per day for acute (single dose). Studies of exposed individuals finds exposures in range of one microgram per kilogram, which is just one percent of NOEL.

With regard to acute exposures, the oral LD50 is in the range of 135 to 160 milligrams per kilogram of body weight. If chlorpyrifos is applied to skin, the LD50 is greater than 2,000 milligrams per kilogram; if it's inhaled, one can't get enough vapor in the air to create an effect. Chlorpyrifos is not genotoxic.

For chronic exposures, chlorpyrifos is not mutagenic, oncogenic, or teratogenic; it does not cause cancer (EPA-designated Class E); it has no reproductive or endocrine effects; and delayed neuropathies (OPIDN) are only possible with superlethal doses.

The current database and available information address the science issues/challenges of FQPA. The weight of evidence evaluation indicates that no additional safety factors are needed and chlorpyrifos uses meet the "reasonable certainty of no harm" standard.

Neurotoxicity and Neuropathology Effects

Chairperson, Marcello Lotti, M.D.

University of Padua Medical School

The staggering complexity of the nervous system hampers the understanding of neurotoxicity. Different types of neuronal connectivity may offer an interpretative frame for neurotoxicology in general and for that of organophosphorus esters (OP) in particular. Three systems could be identified. A long hierarchical system which is exemplified by the motor and sensory pathways, a local circuit system with cells of similar functions and local circuits with larger spatial domains, acting away from the cells of the local circuits. This neuronal organization gives rise to different types of susceptibility. If an axon is affected the entire function of either motor or sensory pathway is lost. However, when cells of local circuits are lost, enormous compensation capability is available. For instance, more than 90% of the dopamine content must be lost in the substantia nigra to get Parkinson's disease. Thus, the likelihood of either failure or compensation of neuronal systems after exposures to neurotoxicants depends, to a large extent, on selective toxicities.

OPs may have quite distinct toxicities when affecting different targets. Some of these toxic effects have a morphological correlate (polyneuropathy) others do not (cholinergic overstimulation). Dose-effect relationships vary for each OP and one toxicity (for instance that causing lethality) may prevent the development of another toxicity. New forms of OP neurotoxicity have been described, particularly in man, although results are not consistent and association with exposure very weak. These include persistent behavioral effects after OP poisoning and other behavioral effects after prolonged low level exposures.

Meaningful interpretation of these studies would be possible when additional targets of toxicity will be identified and their sensitivity compared with that of already known targets. Only in this way will we understand neurotoxic risks and perhaps shed some light on the circuit functions of neuronal connectivity.

Chlorpyrifos Exposure and Human Health

Marcia van Gemert, Ph.D.
van Gemert & Hauswirth, LLC

An eight-member multidisciplinary panel of independent scientists was convened by Dow AgroSciences in cooperation with the EPA to provide an independent appraisal of the scientific evidence concerning chlorpyrifos's potential impact on human health. The panelists had expertise in epidemiologic study design and analysis, occupational epidemiology, poison control surveillance, exposure assessment, neurologic disease, and neurobehavioral assessment.

The panel was asked to evaluate the available human data, to develop a list of recommendations for epidemiologic studies (including suitable endpoints and populations and the pro's and con's of each approach). The topics investigated included exposure, poisoning surveillance data, occupational assessments, immunologic disorders, and multiple complaints. The panel assessed the quality of the existing database to evaluate cause-and-effect relationships between chlorpyrifos and specific diseases, then rated the persuasiveness of the existing data on each of the adverse health outcomes reviewed under two different scenarios: chronic low dose, which might occur in manufacturing and professional application of the product, and acute high dose, which may occur in an intentional or unintentional poisoning episode. Two neurologic outcomes were examined: OPIDN (organophosphate-induced delayed neuropathy) and sensory polyneuropathy. The panel then considered whether further studies should be undertaken on exposed populations in order to evaluate the risk of specific potential adverse effects, such as cognitive and affective disorders (neurobehavioral outcomes) or birth defects.

The panel concluded that 1) OPIDN appears to be confined to extremely high doses, with minimal relevance to public health considerations; 2) insufficient evidence exists to warrant further investigation of sensory polyneuropathy from chronic low doses; 3) behavioral outcome (cognition) is the most suspect for possible chlorpyrifos-induced effects; 4) affective disorders should be evaluated if cognitive dysfunction was studied; 5) no credible human data exist on immunologic disorders; and 6) further study of biological plausibility has no value.

The panelists voted 5 to 3 against the recommendation that further epidemiologic studies be undertaken on populations exposed to chlorpyrifos with respect to potential adverse effects. The majority opinion was based on their assessment that the literature reviewed provided little or no scientific evidence that chlorpyrifos exposure causes harm to human health, other than its known cholinergic effects associated with acute poisoning. The three voting in favor of further research felt that more evidence was needed to preclude the possibility of adverse effects to human health from exposure at levels associated with the manufacture or professional application of chlorpyrifos.

Incident Data

Richard Kingston, Ph.D.
University of Minnesota

Incident data consider the marketplace as the laboratory and look at effects that might actually be witnessed with individual products. Three methods of capturing incident data are: public poison centers (PPCs); dedicated company stewardship programs with toll-free, 365-day nationwide coverage; and anecdotal reports from medical literature.

The PPC approach collects a basic data set on each case. This method gives a good overall picture of the marketplace and provides a very sensitive indicator of potential toxicity. However, the service is primarily triage focused, like a 911 center. It is an anonymous, voluntary reporting system that relies on translation of layperson descriptions. Its database focuses mainly on single, acute exposure incidents – less than 3 percent are chronic effects. Both harmless and serious incidents may go unreported. Data collection is tailored to product application and general use characteristics of that particular substance. It is difficult to assess data integrity.

PPCs provide a snapshot of product availability and what ends up being reported. Data are more "sensitive" than "specific" and may best be utilized to characterize or confirm product safety. PPCs are an excellent tool to develop toxicity hypotheses.

A 10-year (1985-94) PPC data summary of outcomes for 36,183 chlorpyrifos exposure-related inquiries found the following: no effect, 27%; minor effect, 25%; moderate effect, 3%; major effect, 0.3%; fatality, 8 (most intentional self harm); case not followed, 31.5%; unrelated effect, 12.5% Incidents involving adverse effects associated with chlorpyrifos were low, with minor outcomes in about 94% of incidents.

Company stewardship programs have several advantages: 1) health professionals responding to inquiries are "specifically" trained on the product, 2) data collection is tailored to the product, its application, and its general use characteristics, 3) individual incidents can undergo further clarification to assess data integrity, and 4) other service offerings (e.g., medical testing) allow more intense scrutiny of reported events

During a 2-year period, the Dow Stewardship Program received 881 total calls, 490 (56%) of them regarding chlorpyrifos. Of these, 185 reported incidents, while 306 were FYI/unrelated. Nine calls had a significant outcome: 1 death, 3 unsuccessful suicide attempts, 1 allergic reaction, 1 exacerbation of an asthmatic condition, 1 spraying in eye, and 1 unintentional ingestion by a baby. As with the PPC data, minor outcomes comprise over 94% of reported call incidents, the majority associated with objectionable odor. Significant outcome incidents are typically the result of intentional/unintentional misuse or suicidal behavior.

In an analysis published in 1992 of 3.8 million pediatric exposure incidents, where a hazard factor of 3 or greater was considered statistically significant, all aggregated chlorpyrifos incidents had a hazard factor of 2.9.

Overview of Neurotoxicity and Neuropathology

Rudy Richardson, Sc.D.
University of Michigan

Chlorpyrifos is a diethyl phosphorothionate, which is metabolized to the active oxon via oxidative desulfuration. A major route of detoxification is hydrolysis catalyzed by A-esterases such as paraoxonase to yield 3,5,6-trichloropyridinol (TCP), which can be used in biomonitoring to assess chlorpyrifos exposure. The mode of insecticidal action of chlorpyrifos is inhibition of nervous system acetylcholinesterase (AChE) by the oxon. AChE is also found in erythrocytes (RBCs) of humans and many other species; its inhibition can be used as a biomarker of exposure. Inhibition of plasma butyrylcholinesterase (BuChE) may also be used as a biomarker of exposure; inhibition of this enzyme is not regarded as an adverse effect. Some organophosphorus (OP) compounds are capable of producing OP compound-induced delayed neurotoxicity (OPIDN) by inhibition and aging of neuropathy target esterase (neurotoxic esterase, NTE) in the nervous system. OP insecticides currently registered for use in the U.S., including chlorpyrifos, are not regarded as a hazard with respect to OPIDN, because their relative inhibitory potency for AChE is much higher than that for NTE. As a consequence of this selectivity for AChE, it is not possible to produce OPIDN following sublethal acute or repeated doses. Young animals are even more resistant to OPIDN than are adults, possibly as a result of the relatively greater plasticity and capacity for repair in the developing nervous system. The resistance of young animals to OPIDN is important to note in the context of FQPA, which makes the opposite default assumption.

Clinical Experience

James Albers, M.D., Ph.D.

University of Michigan

The organophosphorus (OP) compounds are a large class of acetylcholine esterase inhibitors that are widely used as insecticides. Acute, high dose exposures are uncommon, usually in the form of manufacturing or application accidents or suicidal ingestion. The resultant acute cholinergic syndrome is well established, with characteristic symptoms and signs attributable to acetylcholine excess. In the absence of substantial hypoxia or hypotension, this acute syndrome is readily reversible.

Certain OP compounds produce subacute and delayed neurological syndromes. In the intermediate OP syndrome, weakness develops several days after acute OP intoxication. This reversible syndrome resembles cholinergic crises seen in myasthenia gravis patients receiving excessive anticholinesterase medications. Organophosphorus induced-delayed neurotoxicity (OPIDN) is characterized by a dying-back (length dependent) axonal neuropathy. This predominant motor neuropathy develops 1 to 3 weeks after acute OP intoxication, producing flaccid weakness of the distal limbs and occasionally mild sensory loss. Recovery takes months to years and is often incomplete with late development of spasticity from myelopathy. More controversial are other proposed neurobehavioral syndromes attributed to acute or chronic OP exposures. In general, they are not-specific and poorly characterized.

Not all OP compounds have similar dose-related neurotoxicity. With respect to chlorpyrifos and human exposure, important questions include: 1) does acute or chronic exposure cause permanent, irreversible damage to the nervous system (brain or peripheral nerves), and 2) if so, what is the relationship between neurotoxicity and the acute cholinergic syndrome?

Review of the peer-reviewed literature for chlorpyrifos identifies few reports of adverse human neurotoxicity. The 32 human exposure citations involving chlorpyrifos include descriptions of acute cholinergic syndromes and other forms of suspected neurotoxicity, as well as unremarkable epidemiological studies of manufacturers. Isolated case reports include descriptions of transient extrapyramidal (movement) disorders, vocal cord paralysis, sensory neuropathy, and neurobehavioral abnormalities associated with chlorpyrifos exposure. Review of the human exposure citations for OP compounds in general includes similar descriptions, based primarily on case report and cross-sectional studies.

The underlying concern raised is that OPIDN is but one OP-associated disorder that represents the worst case situation in a spectrum of neurologic manifestations. In response to this concern, the few reports of sensory neuropathy represent an important observation because sensory axons may be involved in OPIDN and because identification of sensory neuropathy should not be controversial. To date, only one report associates chlorpyrifos exposure with sensory neuropathy in the absence of a severe cholinergic syndrome. However, heterogeneity of the clinical and

electrodiagnostic information makes the association of a chlorpyrifos-induced sensory neuropathy suspect, and sensory neuropathy is unlikely to be a sensitive indicator of OPIDN or OP intoxication.

In summary, the available scientific evidence involving human chlorpyrifos neurotoxicity does not support a casual relationship with a ny neurologic or neurobehavioral syndromes in the absence of severe, acute cholinergic toxicity. At best, the possibility of previously unrecognized chlorpyrifos-induced neurotoxicity associated with acute or chronic exposure remains an unproved hypothesis for further study. A July, 1997 multidisciplinary panel report arrived at a similar conclusion. Their report identified little scientific evidence of adverse effects other than cholinergic toxicity with acute chlorpyrifos poisoning, although existing studies had insufficient power to preclude the possibility of adverse neurobehavioral effects at levels associated with manufacture or professional application.

Developmental Effects

Chairperson, Robert Brent, M.D., Ph.D., D.Sc. (Hon)

DuPont Hospital for Children

"Teratogenic effects" due to environmental agents are primarily threshold effects which means that every known teratogen has a no-effect level (NOEL). Once the threshold is reached, increasing the dose increases both the severity and frequency of reproductive effects. Below the threshold you still have the baseline reproductive problems in the population. In the human this would mean that there is the baseline incidence of prematurity, growth retardation, congenital malformations, stillbirths and infertility that are unrelated to a particular environmental exposure.

The other important principle in evaluating the teratogenicity and reproductive effects of an environmental agent is that the time of exposure is extremely important. Some teratogens have a very narrow period of exposure where they can produce their effects. For instance, thalidomide has its major effects from approximately the 22nd day postconception to the 36th day postconception in the human. Other teratogenic agents, primarily cytotoxic agents will have a broader effect where they can interfere with growth and development. While most major malformations involving entire organ systems are sensitive during the period of early organogenesis, approximately the 18th to 40th day, other organ systems maintain their sensitivity over a much longer period of time. For instance the maximum time for agents which affect the central nervous system is from approximately the 8th to 15th week. This is the time when neurons proliferate and migrate to their perspective parts in the brain.

The third principle is that teratogenic agents produce a confined constellation of malfunctions that in a sense identifies the agent. While it is true that genetic diseases can mimic teratogenic effects and vice versa, it is also true that teratogenic agents cannot produce every malformation and that in many instances one can rule out a teratogenic agent by the nature of the malformations observed in the population or in the individual.

The other important principle is that teratogenic agents do not function over many orders of magnitude. Usually the no effect level and the lethal effect may only span one or two orders of magnitude with regard to the dose that is administrated to the population.

Finally, it is important to realize that the human population has a reproductive history that indicates that approximately 30 percent of pregnancies will end up with either genetic disease in the offspring, congenital malformations, or spontaneous abortions unrelated to an environmental exposure.

Finally, it is of interest that in the in vitro genotoxic test, chlorpyrifos does not appear to have mutagenic potential. This would indicate that it has little cytotoxicity, especially at the exposures that the population might receive and, therefore, one of the most important mechanism for teratogenesis would be missing with this particular agent.

Potential Susceptibility of Young Animals

Carey Pope, Ph.D.
Northeast Louisiana University

Are young animals (i.e., Sprague-Dawley rats) more sensitive than adults to chlorpyrifos? Most studies use acute lethality as the endpoint. Generally, young animals are more sensitive to lethality from high, acute organophosphate exposures. Is this difference an appropriate endpoint for regulating pesticide use?

In the real world, low-dose, repeated exposures to pesticides occur, particularly dietary exposures. Aside from acute sensitivity based on lethality, more subtle neurochemical alteration is probably a more realistic endpoint for regulating pesticides.

It is hypothesized that age-related differences in chlorpyrifos sensitivity vary markedly with the nature of exposure. Differences in biotransformation are important in high-dose exposures. Differences in AChE recovery are important in lower, repeated-dose exposures. Adaptive responses (e.g., autoreceptor) are more important in high-dose exposures.

Young animals may be more sensitive to acute, high-dose chlorpyrifos exposures – this is biotransformation limited. They are less sensitive to repeated intermittent exposures, their acetylcholinesterase enzyme recovery is more robust, preventing accumulative effects of the repeated exposures. With repeated, lower-level daily exposures, relatively similar neurochemical changes were noted in both age groups, probably due to a balance between differences in biotransformation and acetylcholinesterase recovery between neonates and adults.

The no observable effect level for signs of toxicity with daily oral chlorpyrifos exhibited a fivefold difference between young and adult, with neonates having a functional NOEL about five times lower than adults (1.5 milligrams per kilogram of body weight per day, versus 7.5 milligrams). There is a 2.4-fold difference in the dose required to inhibit 50 percent of brain cholinesterase activity in the neonatal animal, compared to the adult.

Cholinergic neurochemical changes in the brain from repeated oral and subcutaneous dosing were similar. After repeated lower level chlorpyrifos exposures, minimal age-related differences in sensitivity to cholinergic toxicity were apparent. There was no apparent differential modulation of brain muscarinic receptors between the two age groups.

Age-related organophosphate toxicity can vary with the nature of exposure (amount, timing). With chlorpyrifos, young animals appear more sensitive than adults to acute, high-dose exposures (biotransformation limited); less sensitive to repeated, intermittent exposures (AchE recovery limited); and relatively similar in sensitivity to repeated, lower level daily exposures.

Recognition of the crucial role of exposure intensity and frequency on age-related differences in toxicity is critical for interpretation of relative susceptibility.

Developmental Neurotoxicity

Jacques Maurissen, Ph.D.
The Dow Chemical Company

In a safety evaluation study, chlorpyrifos was administered to Sprague-Dawley rats via once-daily gavage to the dams. The dosage period started on gestation day 6 and went continuously through lactation day 10, with doses ranging as high as 5 milligrams per kilogram of body weight per day.

When maternal behavior was examined, there were several clinical signs of cholinergic toxicity (e.g., fasciculations, hyperreactivity, hyperpnea). No effects were seen below the 5 milligram high dose. Decreased body weight gains and slightly reduced food consumption were observed in dams. Reproductive indices were not affected.

Pup mortality increased, while their body and brain weights and motor activity decreased. There was no effect on the rate of acquisition of long-term memory or on short-term retention or habituation (measured by either a motor activity test or auditory startle test).

On gestation day 20, when the high-dose (5 milligrams per kilogram) group blood CPF concentration was compared with the intermediate (1 milligram per kilogram) group's, the difference in effect was on the order of 40 fold, not the fivefold difference in dosage.

Maternal protection was operating, as chlorpyrifos levels in fetal blood were half to a third that in the dam's. The research concluded that low doses (0.3 milligram) of chlorpyrifos had no effect on brain cholinesterase of dams and no other toxic effects on dams or pups. Intermediate doses (1 milligram) affected brain cholinesterase in the dams but not in pups. High doses (5 milligrams) have tremendous inhibition of brain cholinesterase, with maternal toxicity and developmental delay in pups but no effect on cognitive functions. The pups exhibit delayed maturation secondary to maternal toxicity, although direct pup toxicity cannot be ruled out. In the absence of maternal toxicity, no effects were seen in the pups. The recovery rate for cholinesterase appears to be faster in pups than in dams.

The chlorpyrifos NOEL for maternal and pup toxicity is 1 milligram per kilogram body weight per day; thus, the compound is not a selective developmental neurotoxicant.

Neurotoxicity and Neuropathology Effects
Developmental Effects
Panel Discussion

Some questions to be considered: What is the most reasonable way to integrate toxicity data to determine an acceptable daily intake, to achieve the statutory requirement that there is reasonable certainty of no harm? Are the data indicative of a lesser, greater, or equal sensitivity of young test animals at dose effect levels typical of human exposure? What data are the most salient in describing the relative susceptibility of young and adult test animals? What is the most appropriate toxic endpoint for the regulation of chlorpyrifos at typical exposure levels? Does the additional tenfold safety factor need to be applied to this toxic endpoint to assure the safety of children and infants exposed to this compound? Do the data justify treating all organophosphates as a class of toxicants with a common mechanism of action? Can high-dose information be used to indicate whether there is a greater or equal sensitivity at a low dose? Is cholinesterase the right biomarker to use as a discriminator between adults and children?

Organophosphates do not present a health hazard from the neurologic point of view as causing specific illnesses. The endpoint is not a public health crisis or problem. Determining whether young animals/people may be more or less sensitive than adults to organophosphate exposure depends not only on the dose magnitude but also on how frequently the organism is exposed. There is no reason to believe that pups are more sensitive to chlorpyrifos.

There are many implicit safety factors already built into the regulatory process. There is no reason to add another tenfold safety factor to the existing data. Can it be demonstrated that what is being measured is injurious and not merely a change that can be quantified?

If no effects are discovered in a multi-generation or teratology or developmental study, developmental nerve toxicity should not be a problem. However, a few recent reviews have found that developmental and teratology study data do not always predict developmental nerve toxicity.

Can the issue of whether there are adverse behavioral or developmental effects be examined by concentrating not on standard or average things but rather by looking for events that are strange and at populations that have particularly high levels of exposure, instead of the general populace? What proportion of the population has a dose that is anywhere near the studies that show effects? It must be confirmed that one is operating in the range of reality when discussing the exposures that people are actually experiencing. There is no compelling evidence for the kinds of endpoints under examination, particularly when one considers realistic dose ranges.

Exposure Conditions

Chairperson, Keith Solomon, Ph.D.
University of Guelph

Measurement of exposures to pesticides from a number of possible sources is critical to understanding the importance of these routes of exposure and to supplying data for calibration of exposure models. Good methods are available for analysis and these are routinely applied to foods and other sources of exposure to the general public. Our experience in Canada has shown that these exposures are frequently (70-80%) below the method of detection limit and that few, if any, are above guideline values. Similarly, routine monitoring of drinking water has shown that concentrations are low with respect to water quality guidelines and some pesticides are rarely detected, even in the raw water. Food residues of pesticides at the farm gate may differ very significantly from those in prepared food that has been stored for a time, that has been washed or that has been cooked. It is important to recognize that simple addition of pesticide MRLs from foods will give a very unrealistic estimate of exposure. These measured values can be usefully applied to exposure models that link to food consumption data for large samples of the population where diversity of food habits is captured and used to derive probabilistic exposure estimates.

The food and water routes of exposure are relatively well understood and it is assumed that all the pesticide residues in the food are biologically available to the consumer. This is not the case with other routes of exposure where exposure is via the skin. The major routes of exposure from residential and landscape pesticide use is through inhalation and skin absorption. While it is reasonable to assume that inhalation will result in complete absorption of the droplet or vapor in the body, penetration of pesticides through the skin is variable, depending on the properties of the pesticide and the actions of the exposed person, such as washing of the skin or the body region exposed. This is also relevant to children and skin or mouth contact with treated surfaces. Recent studies with chlorpyrifos and other pesticides have shown that, even shortly after spraying, surfaces such as vinyl will dislodge relatively small amounts of pesticide to contact with human skin. Dosimeter studies of skin exposure can therefore give higher estimates of body dose and biological monitoring is the preferred monitoring method, where the chemistry allows its use. Measurements of exposures that focus on other routes related to home and garden use of pesticides are rare and generate considerable uncertainty. They must be interpreted with caution as they are often based on worst-case studies where contact activities are maximized. Results from these studies require good knowledge of activity patterns in the target group if they are to be interpreted properly.

Acute Dietary Assessment

Heidi Bolles, B.A.
Dow AgroSciences LLC

The most-refined (Tier 4) estimates of exposure (residue times consumption) indicate a wide margin of safety for current uses of chlorpyrifos. The combination of more-realistic assessments and real-world data shows the level of risk for chlorpyrifos to be well below the “full cup,” which is inherently conservative

Chlorpyrifos is unique among pesticides in that market basket data have been collected, which permit higher-tier assessment. Higher-tier assessments have more-complete models, more real-world data, fewer assumptions, and are more realistic. These point-of-purchase data, collected in 1993-94, represent over 1500 samples from 200 stores nationwide and focus on children- and infant-specific foods.

Things happen to food before it is consumed. At each step, beginning when a crop is treated in the field and ending when it’s prepared, cooked, and eaten, pesticide residues are declining. In apples, for example, chlorpyrifos residues decrease 29 fold (from 1.5 to 0.052 ppm) between Tier 1 (tolerance, legal limit, assumes 100% probability of encountering residue) and Tier 4 (ready-to-eat, grocery store data).

There are two kinds of dietary risk assessment: chronic exposure (over a lifetime) and acute exposure (1-day consumption of food and water, single ingestion exposure to pesticide residues). Toxicological studies have found a NOEL (no observed effect level) for chlorpyrifos of 30 ug/kg body weight per day (chronic exposure), 100 ug/kg (acute). Using a factor of 10 to account for human variability, the regulated “risk cup” is 3 ug/kg body weight per day (chronic), 10 ug/kg (acute).

Residential Exposure

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Chlorpyrifos is one of the “grandfathers” of active ingredients in terms of understanding residential exposure. Because it is so well studied, its exposure database consists of information having good quality, quantity, adequacy, reliability, and reproducibility. This allows evaluation of specific subpopulations and development of predictive models that can be validated.

Chlorpyrifos studies are relevant to the multiple residential exposure pathways and routes for both adults and children. The research is relevant to key product categories and use patterns and is representative of potentially exposed populations. Multiple studies by industry, academic institutions, and government agencies allow comparison and validation. The database serves as a credible basis for predictive model development and provides a high degree of certainty to support risk management decision making.

Key sources of residential exposure to chlorpyrifos are termiticide, crack and crevice (ant, roach), and lawn and garden applications. People vary in how they use the product, when they use it, and where they use it. Use/usage information is a very important component that needs to fit into temporal modeling. Exposure to chlorpyrifos occurs during application (dermal, inhalation) or post-application (inhalation, dermal, incidental ingestion via hand-to-mouth transfer).

Applying the exposure database to quantitative assessment involves making measurements relevant to typical product use conditions; linking product use with post-application exposures under a variety of residential conditions and human activity patterns; addressing subpopulations such as applicators and children; and examining plausible pathways and routes of exposure.

Exposure means contact with an agent as measured by the amount available at the biological exchange boundaries (e.g., lungs, skin, GI tract) during some specified period of time. Absorbed dose is the amount of agent that diffuses or is transported across the biological exchange boundaries as a function of exposure duration.

Although biological monitoring is considered the “gold standard,” it has limitations. To develop predictive models useful for routine decision making, both biomonitoring data and controlled experiments are needed, to understand the transport and fate of the compound and exposures relative to activity patterns. Based on biomonitoring survey data, the typical estimated absorbed dose for adults and children associated with key uses of chlorpyrifos ranges from nondetectable to about 2 ug/kg/day. Based on predictive modeling, the absorbed dose ranges from nondetectable to approximately 10 ug/kg/day. Thus, for residential exposures, the chlorpyrifos database provides a credible basis for predictive model development.

Aggregate Exposure Assessment and Biomonitoring Data

Brad Shurdut, M.S., J.D.
Dow AgroSciences LLC

When a pesticide has multiple uses, an individual may be exposed through many pathways (respiratory, dermal, incidental ingestion), including chronic dietary exposure and nondietary sources (lawn care, indoor and structural pest control). Aggregate assessment attempts to merge exposure data by looking at all routes, examining the timing, seasonality, and duration (residuality) of home pesticide applications to determine exposure concurrency. It is essential to get a realistic assessment of exposures in the real world through the temporal allocation of events.

The theoretical population used in aggregate assessment includes all routes of exposure for primary uses: a person eats foods from treated crops, lives in a home treated for termites, treats the lawn (then re-enters the area), and applies crack and crevice spray (then re-enters the rooms). This subpopulation represents between 0.001 and 9 percent of the US population.

The range of exposures for each use pattern has been developed using the chlorpyrifos database. Results from aggregate assessment have been compared to meaningful population-based measurements collected by third parties. Given all data on exposure levels in the US population, there is a low probability that a member will experience exposures near NOEL (no observed effect level). This translates to a reasonable certainty of “no harm” -- the highest measured absorbed doses and aggregate exposure estimate are well below conservative toxicological endpoints.

Aggregate exposures from chlorpyrifos primary use patterns result in low risk for the user subpopulation. Data from national programs (chlorpyrifos has historically been measured as part of biological monitoring) enhance the confidence of results described with aggregate assessment. These biological monitoring samples collected from the U.S. population suggest that maximum aggregate exposures are generally less than a single exposure anticipated from a single use pattern.

Exposure Conditions

Panel Discussion

Available exposure data are more than adequate to provide a reliable estimate of real-world exposure to chlorpyrifos. An extremely flexible and diverse data set exists for chlorpyrifos, translating to a large, robust database over 10 years in development, among the top five available for pesticides. Researchers have worked with growers to understand how they are using the product, have performed a market basket survey, and specifically have focused on children's exposures. The chlorpyrifos database provides an excellent basis for regulatory agencies to develop and evaluate predictive models that can be extended to other active ingredients.

However, improvements can be made. Better data are needed through time to show what's happening on given days, to get at the simultaneous or concurrency issue of chlorpyrifos use. Task forces are developing exposure monitoring databases for the residential environment, outdoor and indoor, and product use and usage information.

Characterizations need to be brought back, to obtain a picture for 100 percent of population, not just an extreme group of users. When researchers have a better understanding of what growers know and what's happening to food between its harvest and ingestion, they can better understand exposure.

The data do not indicate that chlorpyrifos exposure levels of the general public create a health concern. General exposure to chlorpyrifos in the environment may be 1/100 of NOEL (no observed effect level) for one of the most-sensitive indicators. Actual exposures may be more than 1000 times less than the dose needed to elicit harmful effects. Extrapolating to the human population from animal models, a 10-fold safety factor has been injected. This is enough to cover variations within population groups and between adults and children.